Clodoveo Ferri

Systemic Sclerosis

Studies

on

- *Etiopathogenesis*
- *Clinical Manifestations*
- *Prognosis*
- *Survival*



The Lungarni of Pisa

L'aspetto di Pisa mi piace assai
più di quel di Firenze.
Questo Lungarno é uno spettacolo
cosi ampio. cosi magnifico,
cosi gaio. cosi ridente. che innamora.
Non ho veduto niente di simile
ne a Firenze ne a Milano ne a Roma.
E veramente non so se in tutta l'Europa
si trovino molte vedute di questa sorta.

Glacomo Leopardi
Pisa 12 novembre 1827

2021

Journal of Autoimmunity 124 (2021) 102727

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Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

ELSEVIER

Insights into the knowledge of complex diseases: Environmental infectious/ toxic agents as potential etiopathogenetic factors of systemic sclerosis

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Potential Environmental Causative Factors of Systemic Sclerosis

Viruses:

- 1999: Parvovirus B19
- 2002: Human Cytomegalovirus
- 2018: Human herpesvirus 6A
- 2020: SARS-CoV-2

Toxic agents:

- 2018: Silica dust

Potential Environmental Causative Factors of Systemic Sclerosis

VIRUSES

Table 1

Systemic sclerosis (SSc): main putative etiological factors, pathogenetic mechanisms and outcomes. VIRUSES.

	Immune system Mechanisms/*Effects*	Ref. No.	Endothelial cells Mechanisms/*Effects*	Ref. No.	Fibroblasts Mechanisms/*Effects*	Ref. No.
Human Cytomegalovirus (HCMV)	**Significantly higher levels of antibodies against HCMV-derived UL94 protein in serum of SSc patients**/*Molecular mimicry between UL94 and self-peptides expressed on endothelial cells and dermal fibroblasts*	[44,50,52]	**Antibodies directed against UL94**/*Recognition of membrane receptors of endothelial cells (NAG-2) with subsequent apoptosis of endothelial cells and expression of genes functionally associated with clinical signs of SSc (molecular mimicry mechanism)*	[44]	**Antibodies directed against UL94**/*Recognition of membrane receptors of dermal fibroblasts (NAG-2) with activation of fibroblasts and subsequent expression of genes functionally associated with clinical signs of SSc (molecular mimicry mechanism)*	[50]
	Significantly higher levels of antibodies against HCMV-derived protein pp65 in serum of SSc patients/*Higher frequency of SSc-associated autoantibodies*	[36,51]	**Detection of viral transcripts in endothelial cells from skin biopsy of a woman with SSc diagnosed after an acute HCMV infection**/*Possible triggering role for HCMV*	[49]	**Increased expression of pro-fibrotic factors**/*Fibrosis induction in fibroblasts*	[72]
	Increase of HCMV-specific CD8$^+$ T cell responses in SSc patients vs healthy subjects/*Statistically significant association with some of the most relevant disease parameters*	[65]			**Increased expression of fibrosis-associated microRNAs**/*Fibrosis induction in fibroblasts*	[73]
Human Herpesvirus-6A (HHV-6A)	**Increased prevalence/titer of anti-HHV-6 U94 antibodies**/*Multiple HHV-6 reactivations?*	[109]	**Increased expression of pro-fibrotic factors**/*Fibrosis induction in endothelial cells*	[109]	***Increased expression of pro-fibrotic factors***/*Fibrosis induction in fibroblasts*	[72]
	Impaired anti-HHV-6 NK response/*Uncontrolled HHV-6 infection and reactivation*	[109]	**Induction of HLA-G**/*Inhibition of angiogenesis*	[106]	**Increased expression of fibrosis-associated microRNAs**/*Fibrosis induction in fibroblasts*	[73]
Parvovirus-B19 (B19V)	**NLRP3 inflammasome activation**/*Immune-mediated inflammatory tissue damages evolving in fibrosis*	[152]	**CACs apoptosis and impaired mobilization**/*Neo-vascularization defects, diffuse microangiopathy, ischemic tissue damages*	[124,148]	**Fibroblasts activation, increased migration, invasiveness and expression of profibrotic factors**/*Fibrosis induction in fibroblasts*	[146]
Retroviruses	**Antibodies to retroviral proteins in sera from SSc patients. Sequence homologies between specific retroviral proteins and the topoisomerase I antigen (target of anti-Scl 70 antibodies)**/*Molecular mimicry*	[16]	**Experimentally induced expression of retroviral proteins in normal human dermal fibroblasts**/*Acquisition of a SSc-like phenotype and production of extracellular matrix proteins*	[16]		

Abbreviations: UL94 (Unique Long HCMV genomic sequence encoded 94 KDa tegument protein); NAG-2 (Novel antigen-2); pp65 (65 KDa tegument phosphoprotein); U94 (HHV-6 unique gene 94 product); NK (Natural-killer cells); HLA-G (Human Leukocyte Antigen-G); NLRP3 (Nod-Like Receptor pyrin domain containing 3); CACs (Circulating angiogenic cells).

1999

PV-B19

Clin Exp Rheumatol. 1999 Nov-Dec;17(6):718-20.

Parvovirus B19 infection of bone marrow in systemic sclerosis patients

C Ferri [1], K Zakrzewska, G Longombardo, D Giuggioli, F A Storino, G Pasero, A Azzi

Persistent PV-B19 infection of bone marrow

- **chronic stimulus** for the immune system
- impaired production of endothelial progenitors by bone marrow mesenchymal stem cells, which may contribute to diffuse scleroderma microangiopathy

First observation of systemic sclerosis following recent cytomegalovirus infection in a young lady with higly probable genetic predisposition to autoimmunity (mother affected by systemic lupus erythematosus)

2002

Systemic sclerosis following human cytomegalovirus infection

C Ferri, M Cazzato, D Giuggioli, M Sebastiani, C Magro

Ann Rheum Dis 2002

HCMV

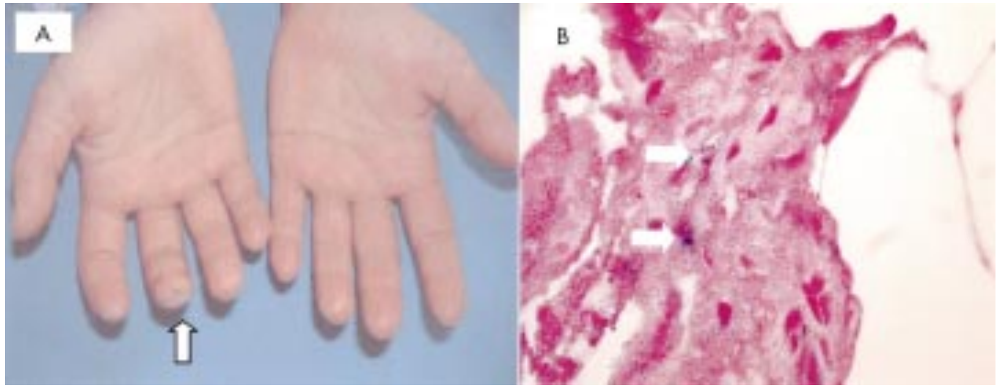


Figure 1 (A) Sclerodactyly and skin ulcer in the third fingertip of the right hand (arrow); (B) skin biopsy: reverse transcriptase-polymerase chain reaction in situ for HCMV RNA showing granular nuclear staining of endothelial cells (arrows).

Nature Medicine **volume 6**, pages 1183–1186 (2000)

Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells

Claudio Lunardi, Caterina Bason, Riccardo Navone, Enrico Millo, Gianluca Damonte, Roberto Corrocher & Antonio Puccetti

2019

HHV-6A

microorganisms

Article

HHV-6A Infection and Systemic Sclerosis: Clues of a Possible Association

Elisabetta Caselli [1,*], Irene Soffritti [1], Maria D'Accolti [1], Daria Bortolotti [1], Roberta Rizzo [1], Gianluca Sighinolfi [2], Dilia Giuggioli [2] and Clodoveo Ferri [2]

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Received: 6 December 2019; Accepted: 20 December 2019; Published: 24 December 2019

Abstract: Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy, excessive extracellular matrix deposition, and fibrosis of the skin and internal organs. Several infectious agents, including human herpesvirus-6 (HHV-6), have been suggested as possible triggering factors, but a direct association is still missing. We characterized 26 SSc patients for the presence of HHV-6 in tissues and blood, the anti-HHV-6 response, HLA-G plasma levels, and KIR typing. Given the prominent role of endothelial cells (EC) in SSc pathogenesis, along with HHV-6 tropism for EC, we also investigated the expression of pro-fibrosis factors in HHV-6 infected EC. Results showed the presence of HHV-6A in skin biopsies, and an increased virus load was associated with disease severity and poor natural killer (NK) response against the virus, particularly in subjects exhibiting a KIR2 phenotype. HLA-G plasma levels were significantly higher in HHV-6A/B-KIR2 positive SSc patients and in vitro HHV-6A infection-induced pro-fibrosis factors expression in EC, supporting its role in the development of the fibrosing process. Our data suggest an association between virus infection/reactivation and disease, opening the way to future studies to understand the mechanisms by which HHV-6A might contribute to the multifactorial pathogenesis of SSc.

La Ghirlandina, Modena



2018

Seminars in Arthritis and Rheumatism 48 (2018) 475–481

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

High serum levels of silica nanoparticles in systemic sclerosis patients with occupational exposure: Possible pathogenetic role in disease phenotypes

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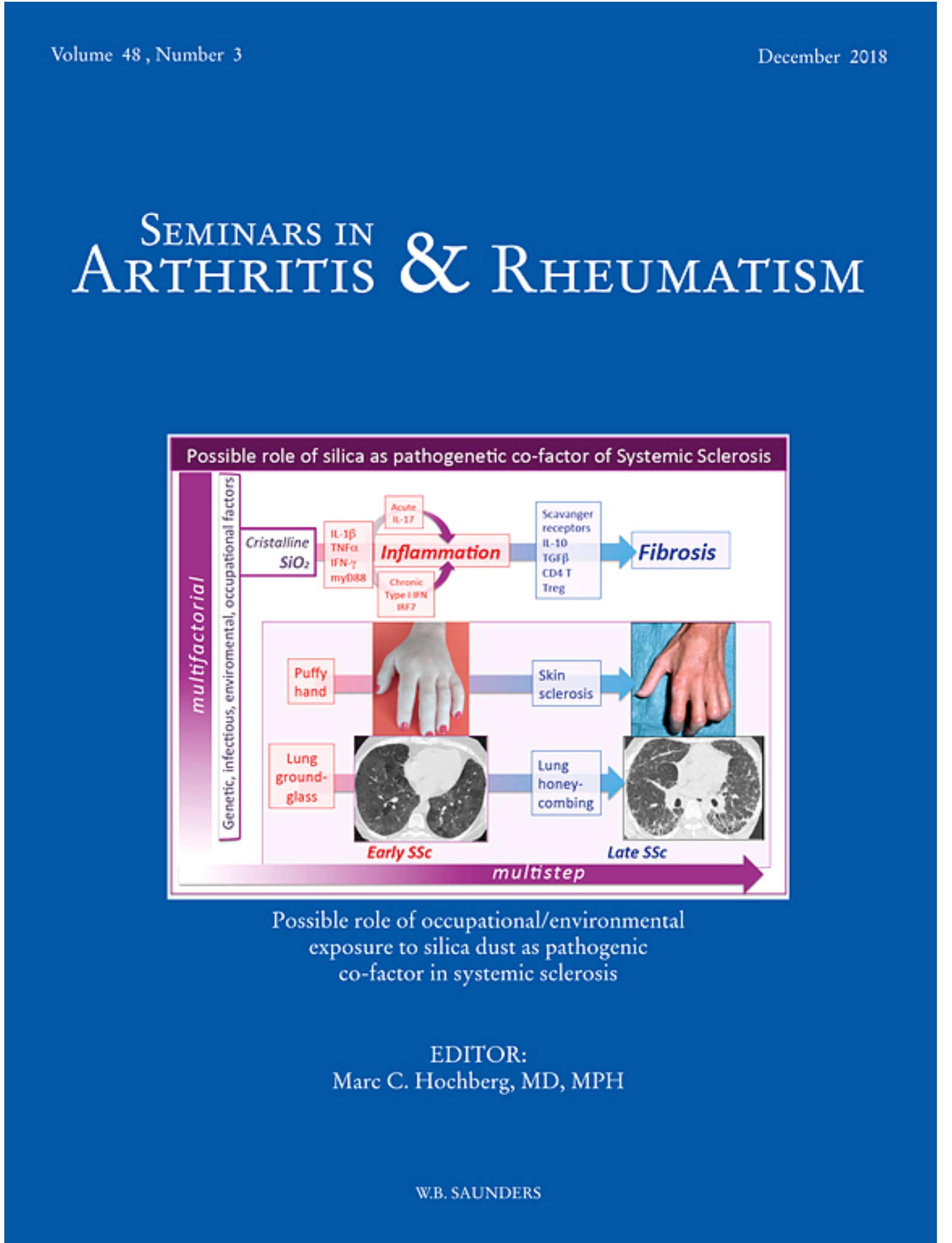
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Etiopathogenesis
Microparticles
Nanoparticles
Interstitial lung fibrosis

Silica

ABSTRACT

Background: Systemic sclerosis (SSc) is an autoimmune systemic disease characterized by diffuse fibrosis of skin and visceral organs due to different genetic, infectious, and/or environmental/occupational causative factors, including the inhalation of silica dust.
Objectives: To investigate serum trace elements including silicon (s-Si) levels in SSc patients living in a restricted geographical area with high density of worksites with silica exposure hazard.
Methods: This case-control study included 80 SSc patients (M:F 10:70; aged 58.4 ± 11.9SD years, mean disease duration 10.1 ± 7.8SD) and 50 age-/sex-matched healthy control subjects consecutively investigated at our University-based Rheumatology Unit. Patients and controls were evaluated for environmental/occupational exposure categories (structured questionnaire), morphological characterization of serum micro-/nanoparticles (Environmental Scanning Electron Microscopy and Energy Dispersive X-ray Spectroscopy microanalysis), and quantitative assessment of trace elements (inductively coupled plasma atomic emission spectroscopy).
Results: Among various categories, only occupational exposure to silica dust was recorded in a significant proportion of SSc patients compared to controls (55% vs. 11%; $p < .0001$). Qualitative analysis showed serum silica micro- and nanoparticles in all exposed patients. Quantitative evaluation evidenced significantly higher s-Si levels in SSc patients versus controls ($p < .0001$); in addition, higher s-Si levels were detected in patients with occupational exposure ($p < .0001$), diffuse cutaneous SSc ($p = .0047$), myositis ($p = .0304$), and/or lung fibrosis ($p = .0004$) compared to those without; notably, the severity of lung fibrosis scoring positively correlated with s-Si levels ($p < .0001$).
Conclusions: The study first demonstrated high s-Si levels in exposed SSc patients; this element might represent a pathogenetic co-factor of more severe clinical phenotypes, mainly diffuse scleroderma with lung fibrosis.



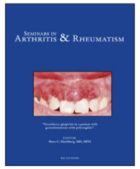
2018 Silica nanoparticles in SSc case-control study

Seminars in Arthritis and Rheumatism 48 (2018) 475–481

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Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit



High serum levels of silica nanoparticles in systemic sclerosis patients with occupational exposure: Possible pathogenetic role in disease phenotypes

Clodoveo Ferri[a,*], Erica Artoni[a], Gian Luca Sighinolfi[a], Fabrizio Luppi[c], Gabriele Zelent[b], Michele Colaci[a], Dilia Giuggioli[a]

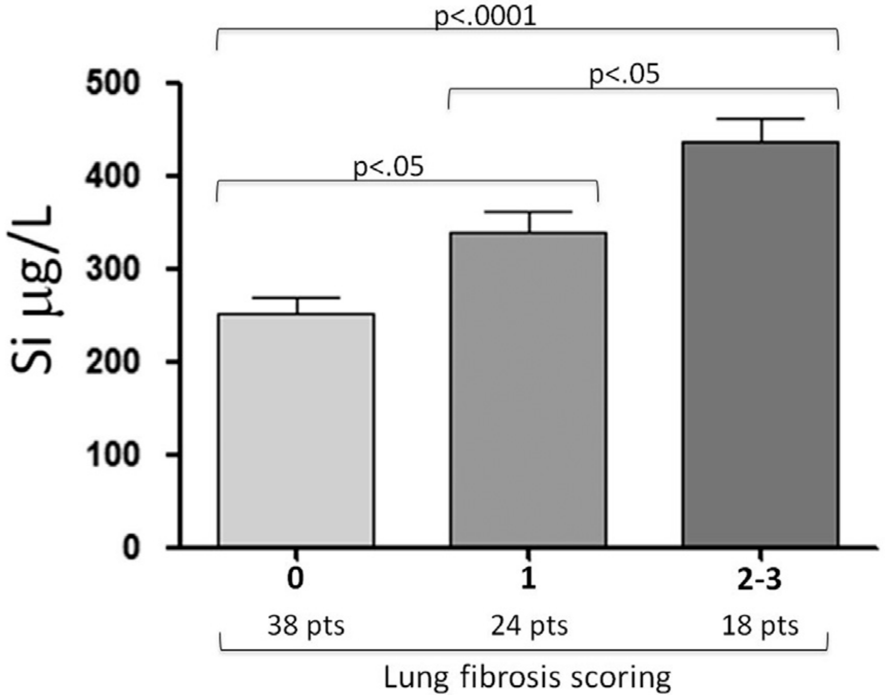


Fig. 3. Systemic sclerosis (SSc) patients with lung fibrosis, detected by high resolution computed tomography (HRCT) in 42/80 (53%) individuals, showed significantly higher levels of serum silicon (s-Si) compared to 38/80 (47%) without ($p < .0001$; Table 2). Moreover, the lung fibrosis scoring significantly correlated with serum silica levels; the highest mean levels of serum silica were found in patients with 2–3° of lung fibrosis. The s-Si levels are expressed as mean ± SEM.

C. Ferri et al. / Seminars in Arthritis and Rheumatism 48 (2018) 475–481

Circulating Silica Nanoparticles correlate with occupational exposure, diffuse cutaneous SSc, myositis, and Lung Fibrosis scoring (HRCT)

Serum micro-/nanoparticles
by Environmental Scanning Electron Microscopy and
Energy Dispersive X-ray Spectroscopy microanalysis,
Quantitative assessment of trace elements
by inductively coupled plasma atomic emission spectroscopy.

Silica nanoparticles

Table 2
Systemic sclerosis (SSc): main putative etiological factors, pathogenetic mechanisms and outcomes. CHEMICALS.

	Immune system Mechanisms/*Effects*	Ref. No.	Endothelial cells Mechanisms/*Effects*	Ref. No.	Fibroblasts Mechanisms/*Effects*	Ref. No.
Silica (Si)	**IL-2 receptor decrease, increase of IFN-gamma, IL-1β, TNF-alfa, IL-6, IL-10 and TGF-β cytokines**/*Immune activation and lymphoproliferation*	[175]	**IL-8 release**/*Cytotoxic effect in mono- and in coculture with A549 alveolar epithelial cells and microvascular cells*	[177]	**Si induced macrophages miRNAs led to myofibroblast transition**/*Critical role in lung damage and fibrosis*	[181]
	NALP3 inflammasome-driven IL-1β increase, Scavenger receptors activation, macrophages apoptosis/*Inflammasome activation, lung inflammation and fibrosis, silicosis*	[178]	**Si O2-induced increased cell proliferation, migration, and changes in endothelial cells; increased expression of mesenchymal markers**/*Lung fibrosis*	[179]	**Silica gel induced collagen and MAP kinase phosphorylation on human dermal fibroblasts**/*Silica gel directly cause fibrotic phenotype*	[182]
	Si NPs trigger cytokine inflammatory response and induce oxidative stress/*Inflammation of human peripheral blood mononuclear cells*	[176]	**Si NPs induced significant calcium mobilization and ROS generation**/*Decreased the viability and damaged the plasma membrane of cultured HUVECs*	[180]	**Si NPs lead to cell necrosis in a dose-dependent manner**/*Fibroblast cell necrosis*	[183]

Abbreviations: IL (interleukin); TGF (transforming growth factor); IFN (interferon); TNF (tumor necrosis factor); NALP (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing); NPs (nanoparticles); ROS (reactive oxygen species); HUVEC (human umbilical vein endothelial cells); miRNA (microRNA); MAP kinase (mitogen-activated protein kinase).



Sunset at Sant'Andrea in Pescaiola

2021

Etiopathogenesis of Systemic Sclerosis

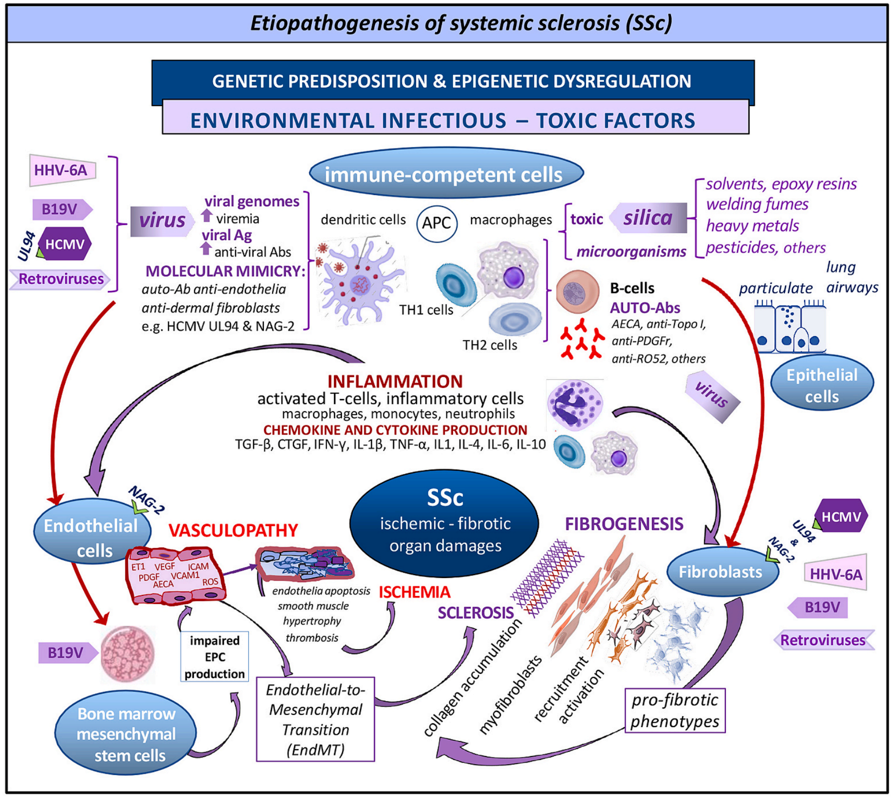
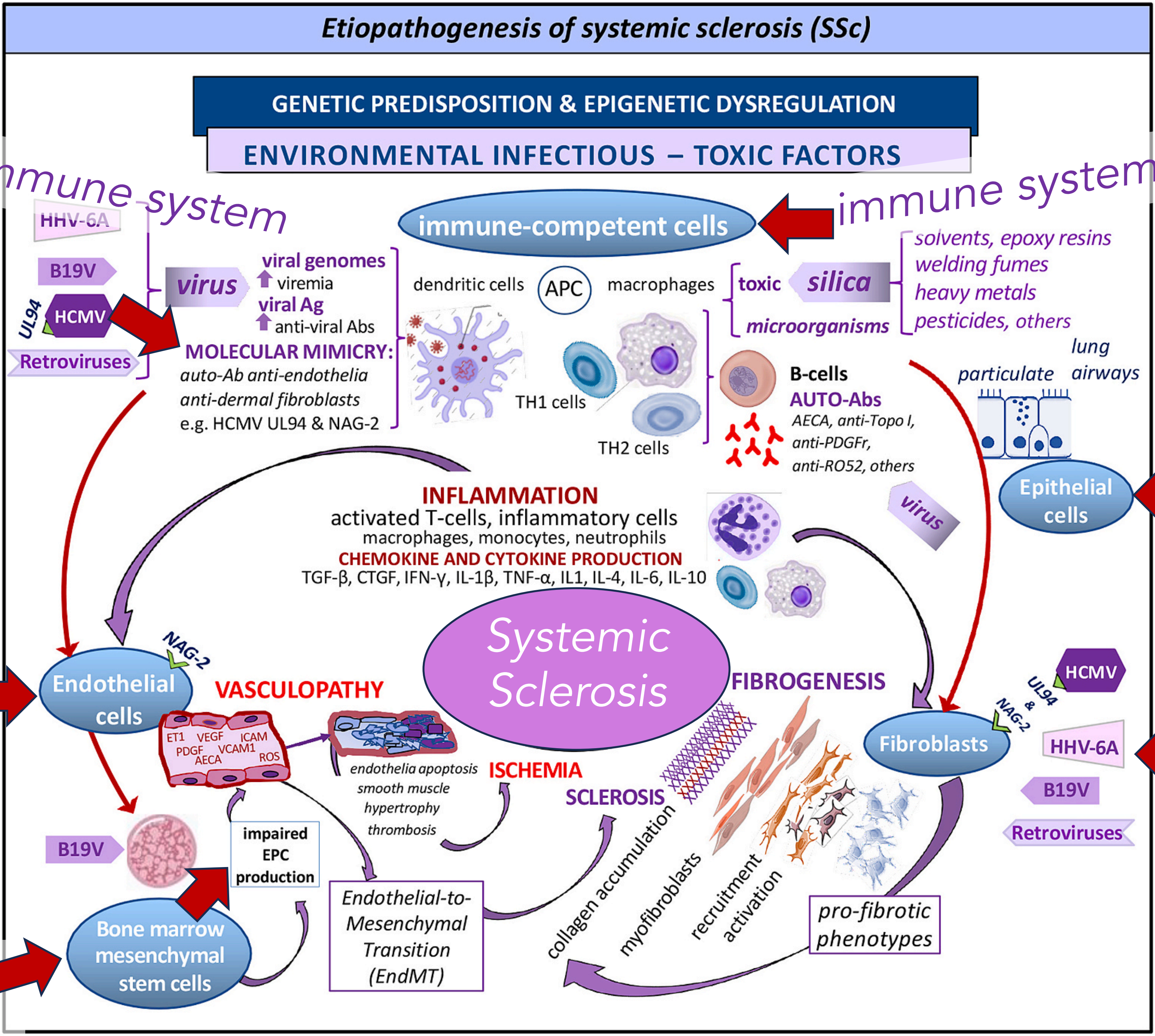


Fig. 1. Putative etiopathogenetic network of systemic sclerosis. The etiopathogenesis of systemic sclerosis (SSc) encompasses a genetically-driven predisposition with the possible contribution of epigenetic modifications, immune-system dysregulation, diffuse microangiopathy, and abnormal collagen tissue deposition by altered fibroblasts. These mechanisms are probably triggered/sustained by variable combination of environmental factors (*i.e.*: infectious/physical/chemicals) through a multistep process. Briefly: **(i) host genetic predisposing factors and epigenetic dysregulation** have a prominent role in the SSc pathogenesis, commonly recognized but not plainly documented; **(ii) remote events** may precede even by years the clinical SSc onset; *i.e.* the exposure to **toxic agents** such as vinyl chloride or silica dust and/or **latent viral infections**, which may affect different target tissues: dendritic cells, macrophages, fibroblasts, endothelial, airway epithelial, immune-competent cells, and extracellular matrix. With respect to viral infections, they may trigger both innate and adaptive immune system with T- and B-lymphocyte activation, antigen-dependent oligoclonal lymphocyte expansion, and specific autoantibody production. The antigen-driven response (**molecular mimicry mechanism**) has been suggested on the basis of sequence homologies between specific viral proteins and self-Ag (*i.e.*: HCMV protein UL94 and self-peptides NAG-2 expressed on endothelial cells and dermal fibroblasts, specific retroviral proteins and topo-I antigen). Molecular mimicry can be responsible for both $CD8^+$ T-lymphocyte and/or autoantibody-mediated endothelial/fibroblast injury, myofibroblast transition, with ischemic and fibrotic organ damage; **(iii) endothelial dysfunction and apoptosis are crucial for both scleroderma vasculopathy and fibrogenesis.** Endothelia are the primarily SSc target cells (reversible digital ischemia of Raynaud's phenomenon is the presenting symptom of SSc in the majority of cases); a direct (viral infection, oxidative stress, toxic agents) or immune-mediated (AECA) endothelial cell damage may lead to severe vascular alterations (sub-endothelial fibrosis, muscular proliferation, and vessel deletion/thrombosis) and ultimately to ischemic lesions. B19V chronic infection of bone marrow might be responsible of impaired production of circulating EPCs with marked consequence for scleroderma microangiopathy. Endothelial to mesenchymal transdifferentiation may contribute to scleroderma fibrogenesis; several proinflammatory and profibrotic cytokines (TGF-β, CTGF, IL-1, TNF-α), chemokines, hypoxia, and autoantibodies (AECA) can be involved in this process; **(iiii) fibroblast transformation into pro-fibrotic phenotypes with collagen hyper-production and tissue accumulation** may be the consequence of direct and/or immune-mediated (molecular mimicry) cell injury; the latter may be promoted by both viral infections and/or toxic agents such as cristallina silica. The myofibroblasts recruited from different sources (resident fibroblasts, bone marrow stem cells, and/or endothelial/epithelial to mesenchymal transdifferentiation) may concentrate at the extracellular matrix and produce excessive collagen accumulation with fibrotic organ damage. *Abbreviations:* HHV-6A: human herpes virus-6A; B19V: parvovirus B19; HCMV: human cytomegalovirus; UL94 (Unique Long HCMV genomic sequence encoded 94 KDa tegument protein); Ag: antigen; Abs: antibodies; vertical violet arrows (↑): increased levels; APC: antigen presenting cells; TH: T helper lymphocytes; AECA: anti-endothelial cell antibodies; anti-Topo I: anti-topoisomerase I (Scl70) Abs; anti-PDGFr: anti-platelet derived growth factor receptor Abs; TGF-β:transforming growth factor beta; CTGF: connective tissue growth factor; IFN-γ: interferon gamma; IL: interleukin; TNF-α: tumor necrosis factor-α; NAG-2 (Novel antigen-2); ET1: endothelin 1; VEGF: vascular endothelial growth factor; ICAM: intercellular adhesion; PDGF: platelet derived growth factor; VCAM-1: type 1 vascular cell adhesion molecules; ROS: reactive oxygen species.

2021

Etio-pathogenesis of Systemic Sclerosis

Ferri C et al.
J Autoimmunity 2021



immune system

immune system

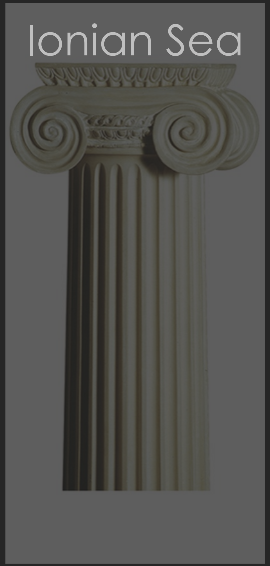
lung airways epithelial cells

endothelial cells

fibroblasts

bone marrow & EPC (endothelial progenitor cells)




Ionian Sea

Systemic Sclerosis: a model of multifactorial and multistep autoimmune systemic disease

2021

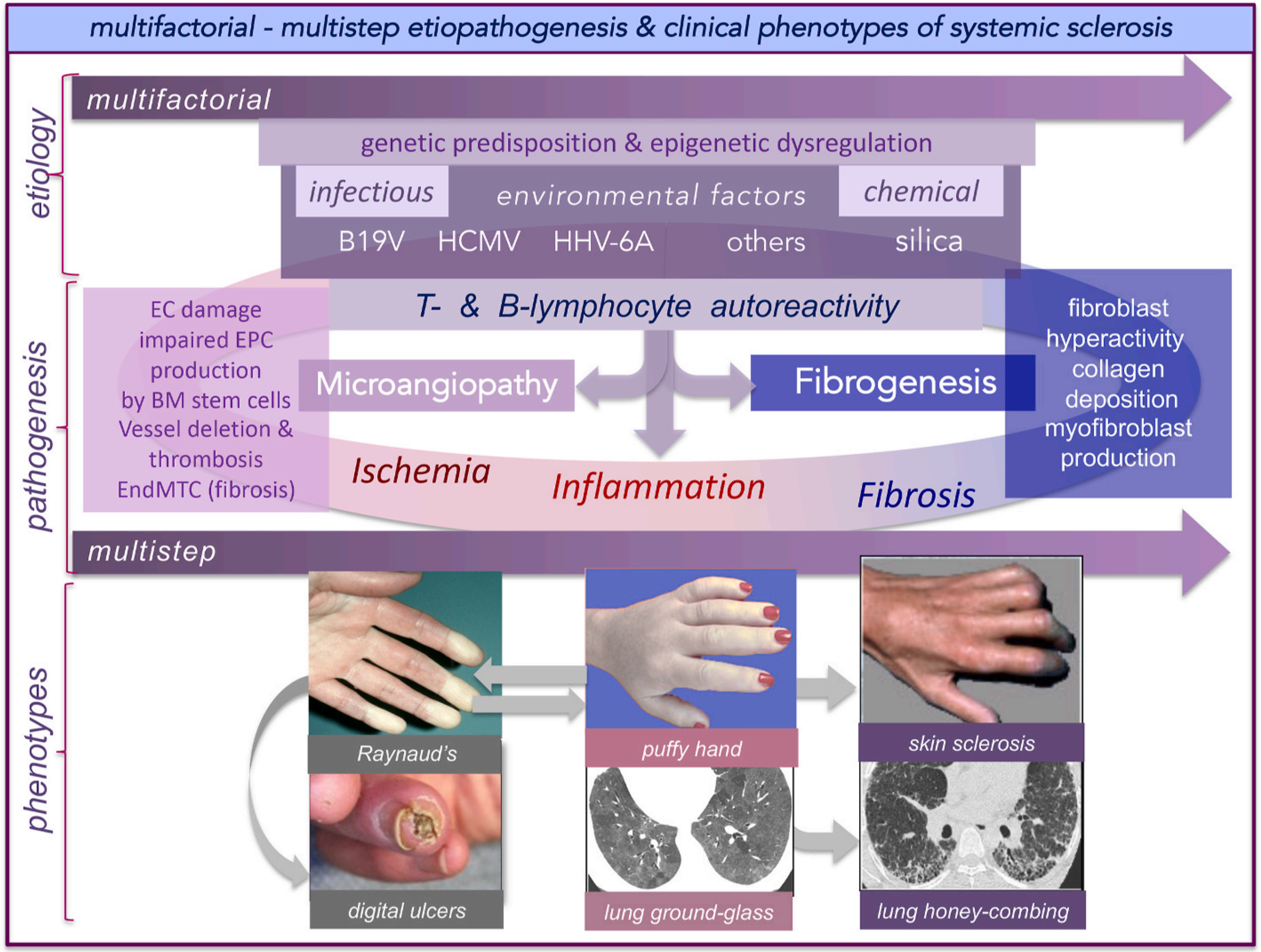
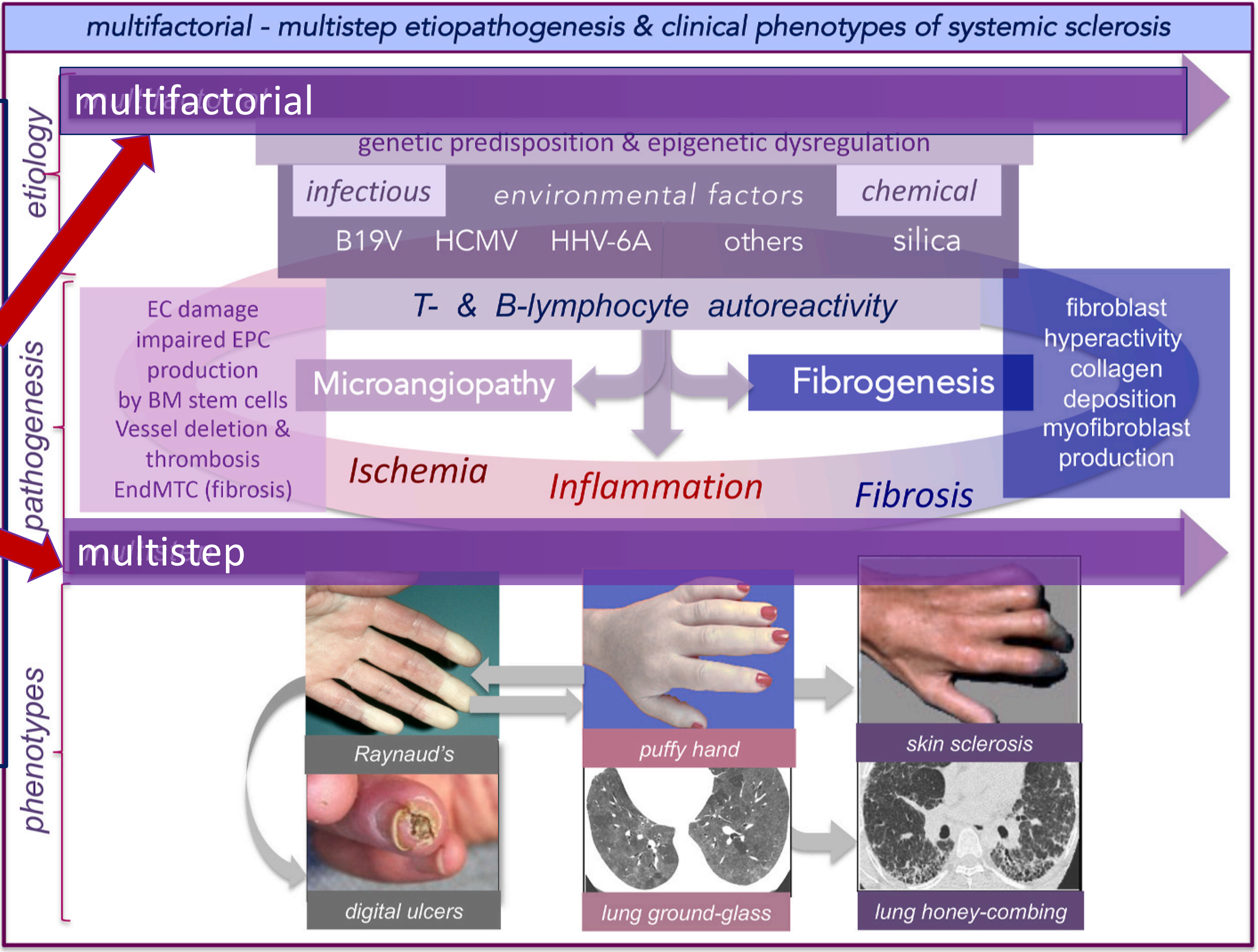


Fig. 2. Multifactorial and multistep etiopathogenesis of SSc with different clinical phenotypes and outcomes. The natural history of SSc commonly recognizes a very early, often subclinical, stage of disease characterized by diffuse micro vessel dysfunction (Raynaud's phenomenon is the early clinical hallmark that frequently precede the beginning of overt disease) and immune-system alterations, followed by progressive vascular manifestations (ischemic lesions of the skin and internal organ), inflammatory immune-mediated clinical features (puffy hands, lung alveolitis with ground-glass opacification), and ultimately more or less severe fibrotic damage (diffuse skin sclerosis with finger flexion contractures, lung fibrosis with honey-combing). This multistep process is often unpredictable in individual patients, it can be the consequence of a variable interaction between hosts' genetically driven autoimmune response to multiple combined/subsequent exogenous causative factors (see Fig. 1). The variable contribution of different etiological co-factors might explain the appearance of different clinical phenotypes and outcomes (skin ulcers, lung fibrosis, pulmonary hypertension, scleroderma renal crisis, etc.) among SSc patients and in the same patient during the course of the disease. *Abbreviations:* EC: endothelial cells; EPC: endothelial progenitor cells; BM: bone marrow; B19V: parvovirus B19; HCMV: human cytomegalovirus; HHV-6A: human herpesvirus 6; EndMT: endothelial-to-mesenchymal transition.

Ferri C et al. J Autoimmunity 2021

2021

Systemic Sclerosis: a model of **multifactorial** & **multistep** autoimmune systemic disease



Ferri C et al. J Autoimmunity 2021



Cropani

Homage to

Domenico Paoletti

humanist and physician

Clodoveo Ferri's great grandfather


FERDINANDO II. PER LA G. DI D. RE DEL REGNO DELLE DUE SICILIE E DI GERUSALEMME,
DUCA DI PARMA, PIACENZA, CASTRO &C. GRAN PRINC. ERED. DI TOSCA. &C.

REGIA UNIVERSITÀ DEGLI STUDI

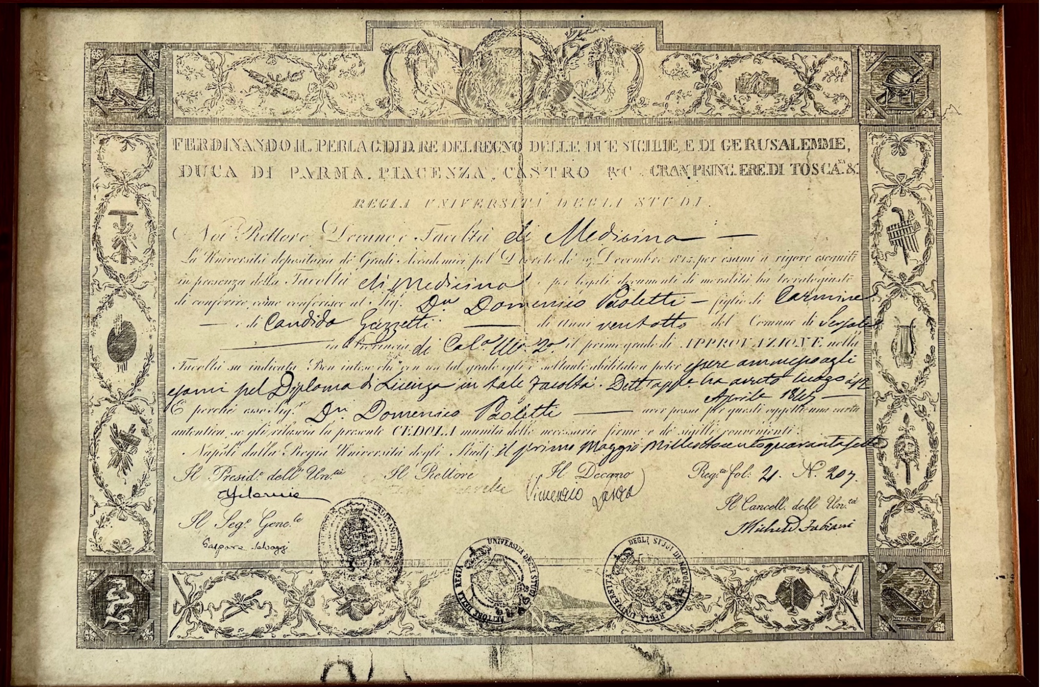
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E perchè esso Sig. Dn. Domenico Paoletti ... si è rilasciata la presente CEDOLA munita delle necessarie firme e de' sigilli convenienti.

Napoli dalla Regia Università degli Studj li ventinove Luglio Milleottocentoquarantasei

Degree in
Belle Lettere & Filosofia,


FERDINANDO II. PER LA G. DI D. RE DEL REGNO DELLE DUE SICILIE E DI GERUSALEMME,
DUCA DI PARMA, PIACENZA, CASTRO &C. GRAN PRINC. ERED. DI TOSCA. &C.

REGIA UNIVERSITÀ DEGLI STUDI

Noi Rettore, Decano e Facoltà di Medicina

La Università depositaria de' Gradi Accademici pel Decreto de' 27 Decembre 1815 per esami a rigore eseguiti in presenza della Facoltà di Medicina per legali documenti di moralità ha creduto giusto di conferire, come conferisce al Sig. Dn. Domenico Paoletti figlio di Carmine e di Candida Gazzetti di anni ventotto del Comune di Sersale in Provincia di Cal. Ult. 2a il primo grado di APPROVAZIONE nella Facoltà su indicata.

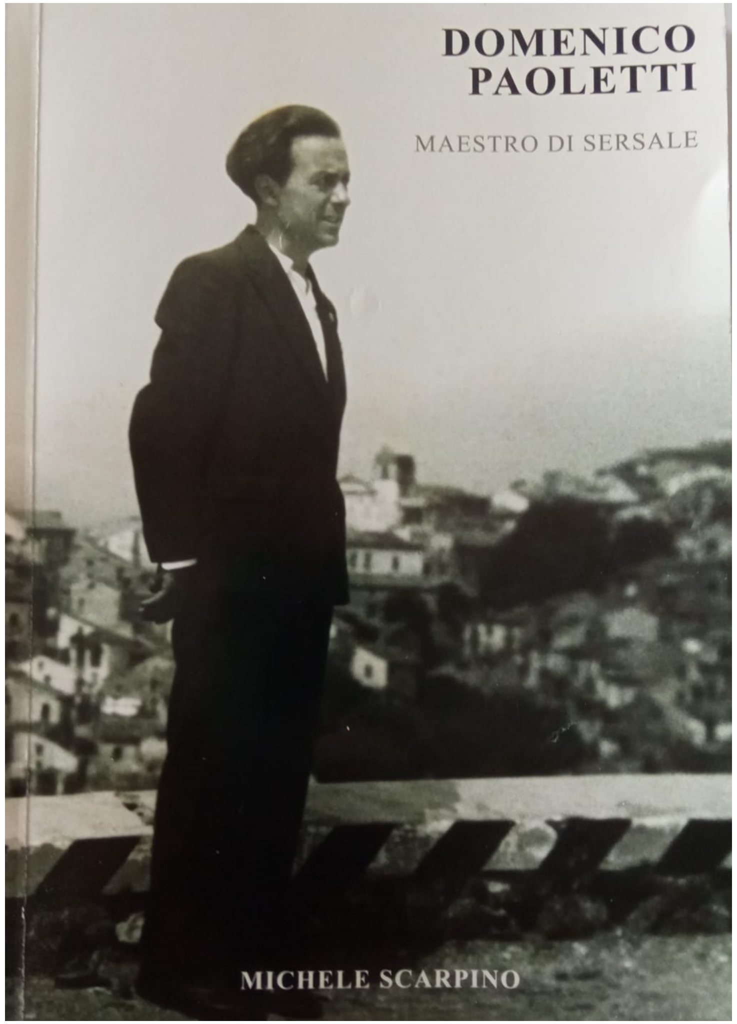
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Napoli dalla Regia Università degli Studj il primo Maggio Milleottocentoquarantasette

Il Presid. dell'Unità — Il Rettore — Il Decano — Il Seg. Gen.le — Il Cancell. dell'Unità

Degree in
Medicina,

University of Naples,
1846-1847



His nephew with the panorama of Sersale

Lancet Rheumatol. 2021 Mar;3(3):e166-e168. doi: 10.1016/S2665-9913(21)00007-2. Epub 2021 Jan 12

THE LANCET
Rheumatology

COVID-19 and systemic sclerosis: clinicopathological implications from Italian nationwide survey study

Ferri et al COVID-19 & ASD Italian Study Group 2021



1,636 scleroderma patients

2021

Higher Prevalence and worse outcome of COVID19 in scleroderma pts vs Italian general population

Prognostic factors

Pre-existing lung inv. → negative

Low dose aspirin → protective

Multifactorial and multistep etiopathogenesis of systemic sclerosis
Possible role of SARS-CoV-2 infection in the worsening of natural clinical course of systemic sclerosis

2023

Possible role of SARS-CoV-2 Infection In Systemic Sclerosis

Journal of Translational Autoimmunity 7 (2023) 100212

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ELSEVIER



Impact of COVID-19 and vaccination campaign on 1,755 systemic sclerosis patients during first three years of pandemic. Possible risks for individuals with impaired immunoreactivity to vaccine, ongoing immunomodulating treatments, and disease-related lung involvement during the next pandemic phase

Ferri C et al. 2023, on behalf of COVID-19 & ASD Italian Study Group

Multifactorial and multistep etiopathogenesis of systemic sclerosis

Possible role of SARS-CoV-2 infection in the worsening of natural clinical course of systemic sclerosis

COVID19 & SSc

2020-23

2025

Worse prognostic factors

- Pre-existing interstitial lung involvement
- Impaired immunogenicity of COVID19 vaccines
- Evolution of ILD from NSIP to UIP pattern after COVID19 episode



Homage to Franz Kafka

Clodoveo Ferri

Systemic Sclerosis

Studies

on

- *Etiopathogenesis*
- *Clinical Manifestations*
- *Prognosis*
- *Survival*

Systemic Sclerosis

- **Prognosis**
- Survival
- Pathomorphosis

1991

Cutaneous and Serologic Subsets of Systemic Sclerosis

CLODOVEO FERRI, LUIGI BERNINI, RICCARDO CECCHETTI, ALESSANDRO LATORRACA, GIORGIO MAROTTA, GIAMPIERO PASERO, ROSSELLA NERI, and STEFANO BOMBARDIERI

Abstract. **The relevance of the extent of skin sclerosis and of other clinicoserological features in diagnosis, severity and prognosis of disease was studied in a large number of unselected patients with systemic sclerosis (SSc). One hundred and fifty-one patients with SSc (126 F and 25 M, mean age 48 ± 14 SD) followed for 5.3 ± 3.2 years were included. Patients were divided into 3 cutaneous subsets: limited (68), intermediate (46) and diffuse SSc (37). Serological markers were detected in 288 patients with Raynaud's phenomenon and other connective tissue diseases (CTD). Limited and intermediate SSc prevailed in female patients while the diffuse subset was more frequent in males ($p < 0.0001$). Duration of Raynaud's phenomenon before disease onset was shorter in the diffuse variant ($p < 0.0001$). A wider cutaneous involvement was associated with more severe forms of SSc. Diffuse subset showed the poorest prognosis at 10 years of followup compared with intermediate ($p < 0.05$) and limited variant ($p < 0.001$). Intermediate SSc seems a distinct variant of SSc on the basis of clinical manifestations and survival. Among serological markers, anticentromere, anti-Scl-70 and antinucleolar antibodies were found in 21, 40 and 27% of the cases, respectively; these were statistically less frequent ($p < 0.0001$) in other CTD. In 83.5% of patients with SSc at least one of these specific markers was recorded. Anticentromere antibodies were correlated to sex (female), limited SSc, calcinosis and telangiectasia. On the contrary anti-Scl-70 was associated with diffuse and intermediate subsets and with more severe SSc manifestations. Our results underline the clinical and prognostic usefulness of cutaneous subsets in patients with scleroderma and the diagnostic value of the serological markers.** (*J Rheumatol 1991;***18:1826–32**)

1991

Prognostic value of the duration of Raynaud's Phenomenon before SSc onset

The shorter the duration of Raynaud's Phen. before SSc onset, the more severe the prognosis of SSc:

the shortest values in patients with diffuse cutaneous SSc and anti-Scl70 positivity

Ferri C et al. J Rheumatol 1991

- **Prognosis**
- Survival
- Pathomorphosis

Table 1. *Epidemiological and clinical variables correlated with SSc cutaneous subsets*

Variables	Total n = 151 %	Limited n = 68 %	Intermediate n = 46 %	Diffuse n = 37 %	p††
Disease duration (yrs)*	10.4 ± 8	13 ± 9	9 ± 7	7 ± 6	NS
Men	17	7	9	42	< 0.0001
Raynaud's	97	98	98	92	NS
Raynaud's dur (yrs)**	5.8 ± 9.8	9.2 ± 11.6	4.1 ± 8.0	0.75 ± 2.4	< 0.0001
Calcinosis	38	43	45	20	NS (<0.06)
Esophageal inv. (rx)	64	49	67	87	< 0.003
Teleangectasia	85	86	88	81	NS
Hypermelanosis	67	51	77	79	< 0.01
Skin ulcers†					
Malabsorbti					
Lung inv					
Heart inv					
Renal inv					

* At end of

† Skin ulcer

Table 3. *Correlations between serological subsets and clinical variables in SSc*

Clinical Variables	ACA+ n = 32 %	Scl-70-ACA- n = 58 %	Scl-70+ n = 61 %	p†
Men	3	17	23	<0.04
Skin sclerosis				
limited	69	57	23	<0.0001
intermediate	22	19	45	
diffuse	9	24	32	
Skin vasculitis	70	74	90	NS (<0.07)
Calcinosis	76	30	22	<0.0001
Telangiectasia	100	78	84	<0.035
Myositis (CPK)	22	61	68	<0.001
Heart inv*	0	13	14	<0.034
Ray. dur. (yrs)**	9.4 ± 12	6.0 ± 11	3.5 ± 7	<0.02

* Severe cardiomyopathy evaluated by ECHOcg; ** Raynaud's duration before other disease symptoms;

† p values refer to comparison between the 3 serological subsets.

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2002

Systemic Sclerosis

Demographic, Clinical, and Serologic Features and Survival in 1,012 Italian Patients

Clodoveo Ferri, Gabriele Valentini, Franco Cozzi, Marco Sebastiani, Claudio Michelassi, Giovanni La Montagna, Arianna Bullo, Massimiliano Cazzato, Enrico Tirri, Franca Storino, Dilia Giuggioli, Giovanna Cuomo, Mara Rosada, Stefano Bombardieri, Silvano Todesco, and Giuseppe Tirri, for the Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSSc)*

TABLE 7. Survival rates in different patient subsets

	10th-Year Survival Rate (%)	p Value
Cumulative from diagnosis	69.2	.0001
Cumulative from SSc onset	87.8	
SSc duration ≤2/>2 yr*	76.9/92.8	.00001
Patients aged ≤35/36–50/>50 yr	79.6/71.6/60.5	.0001
Male/female	53.2/71.6	.00001
Limited/intermediate/diffuse	78.3/65.5/52.2	.00001
Limited/diffuse	75.1/53.4	.00001
Raynaud duration ≤1/>1 yr	67.9/73.4	.0164
Lung involvement +/−	64.9/80.6	.00001
Heart involvement +/−	59.1/77	.00001
Renal involvement +/−	34.8/74.6	.00001
Lung & heart & renal involvement +/−	12.6/86.5	.00001
Anti-Scl70‡ +/−	72.2/80.8	.0525
ACA‡ +/−	85.9/72.7	.0004
ANoA‡ +/−	72.6/80.3	NS
Patients recruited 1955–85/1986–99	60.6/76.8	.0001

*Survival calculated from disease onset in patients recruited after 1985.
‡Survival calculated from diagnosis in patients recruited after 1985.

The shorter the duration of Raynaud's Phenomenon before the SSc onset, the more severe prognosis of SSc
(10th year survival)
as previously observed in Ferri C, J Rheumatol 1991

Systemic Sclerosis

- **Prognosis**
- Survival
- Pathomorphosis

- **Prognosis**
- **Survival**
- Pathomorphosis

2002

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Systemic Sclerosis

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Summary

In this multicenter, retrospective study we evaluate the clinico-epidemiologic and prognostic features of a large Italian systemic sclerosis (SSc) series (1,012 patients, 897 females and 115 males; mean age at presentation, 50.5 yr ± 13.8 SD; mean follow-up, 7.1 yr ± 5.7 SD) recruited between 1955 and 1999 at 3 university-based rheumatology units, from the north (University of Padova), center (University of Pisa), and south (University of Napoli) of Italy. Limited cutaneous SSc was the most frequent subset with the best prognosis independent of the classification used, based on skin sclerosis extent (2- or 3-subset models). The percentages of various organ involvement significantly increased at the last patient evaluation. The progression of the disease during follow-up was mirrored by the constant decrease in the cumulative survival rates (Kaplan-Meier method) calculated at the 10th and 20th year from diagnosis (69.2% and 45.5%, respectively, $p < .00001$); the observed SSc survival rates were significantly lower than those expected in the Italian general population ($p < .00001$).

Among SSc patients, significantly worse prognosis was observed in the diffuse cutaneous subset ($p < .00001$), in male gender ($p < .00001$), and in patients with lung ($p < .00001$), heart ($p < .00001$), and renal involvement ($p < .00001$). A shorter duration of Raynaud phenomenon before the scleroderma onset was correlated with worse outcome ($p < .0164$). With regards to serologic markers, the presence or absence of anti-centromere antibody was an important prognostic indicator (85.9% vs 72.7% 10th-year survival, respectively; $p < .0004$). Univariate and multivariate analysis by Cox proportional hazard regression model further confirmed the results of survival study: the mortality risk was significantly increased in male patients; in patients with diffuse cutaneous SSc; in patients with lung, heart, and kidney involvement; and in patients with abnormally high erythrocyte sedimentation rate (ESR) (>25 mm/h) evaluated at patient enrollment. Thirty percent of patients died during the follow-up period; the most frequent causes of death were cardiac (36%) and lung (24%) involvement, and cancer (15%). Deaths were definitely or possibly related to SSc in 36% and 52% of cases, respectively. Renal involvement was a relatively rare complication in Italian SSc patients; comparable features were observed in other SSc populations from the Mediterranean area.

Patients recruited after 1985 showed a significantly better 10th–year survival rate compared with subjects referred before 1985 (76.8% vs 60.6%, $p < .0001$). Comparable survival rates have been reported in recent studies on SSc series from other countries. This finding could be related to the wider recruitment of mild-to-moderate clinical variants at specialist centers, which better reflects the entire scleroderma spectrum, and, not secondarily, to the possible contribution of recently available therapies.

Proposed Classification Criteria of Systemic Sclerosis

Table 1. Classification criteria and diagnostic parameters of systemic sclerosis

Preliminary Classification Criteria* **1980**	Main diagnostic parameters **2002**
Major Criterion	Proximal skin sclerosis
Proximal scleroderma	Sclerodactily
Minor Criteria	Raynaud's phenomenon
Sclerodactly	Digital pitting scars
Digital pitting scars	Bibasilar pulmonary fibrosis
Bibasilar pulmonary fibrosis	Esophageal dysfunction
	Telangiectasias
	Calcinosis
	Capillaroscopic SSc pattern
	Serum autoantibodies°

*American College of Rheumatology (formerly ARA) 1980 Criteria (ref. 32): the major criterion or any combination of 2 or more minor criteria were found in 97% of definite SSc patients (sensitivity) and in 2% of comparison case (98% specificity). Localized scleroderma and pseudoscleroderma disorders represent criteria of exclusion.

°anti-Scl70, anti-centromere, anti-nucleolar antibodies

+ anti-RNAP3

Ferri et al. Medicine 2002

Diagnostic value of capillaroscopy & SSc specific autoantibodies

Proposed Classification of Raynaud's Phenomenon

2002

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	Telangiectasias
	Calcinosis
	Capillaroscopic SSc pattern
	Serum autoantibodies†

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†Anti-Scl70, anti-centromere, anti-nucleolar antibodies.

TABLE 2. Approach to apparently isolated Raynaud phenomenon

1. Exclusion of other conditions
2. Accurate history and complete physical examination to identify any sign or symptom of connective tissue disease (arthritis, dysphagia, telangiectasias, digital ulcers, or pitting scars, calcinosis)
3. Nailfold capillaroscopy
4. Autoantibody detection

Raynaud phenomenon (RP) classification	
Type I:	Primary, isolated RP
Type II:	Suspected secondary RP. Presence of 1 or more clinical, serologic, or capillaroscopic alterations not sufficient for diagnosis of definite disease
Type III:	Secondary RP

Homage to Antoine Lavoisier

...a great scientist
sacrificed
on the altar of the
Goddess Reason



"To remove
his head the crowd needed
only a moment;
a century will not be enough
to reproduce it"

Joseph-Louis Lagrang

1985

Prognostic role of heart involvement in SSc patients

Noninvasive evaluation of cardiac dysrhythmias, and their relationship with multisystemic symptoms, in progressive systemic sclerosis patients.

Ferri C, Bernini L, Bongiorni MG, Levorato D, Viegi G, Bravi P, Contini C, Pasero G, Bombardieri S.

Arthritis Rheum. 1985 Nov;28(11):1259-66.
doi: 10.1002/art.1780281110.

Systemic Sclerosis

- **Prognosis**
- **Survival**
- Pathomorphosis

1997

Prognostic role of Heart involvement in SSc patients

Br J Rheumatol 1997 Jun;36(6):669-76.

Autonomic dysfunction in systemic sclerosis: time and frequency domain 24 hour heart rate variability analysis

C Ferri[1], M Emdin, D Giuggioli, C Carpeggiani, M Maielli, A Varga, C Michelassi, G Pasero, A L'Abbate

doi: 10.1093/rheumatology/36.6.669.

Abstract

To evaluate the autonomic nervous control of the heart in patients with systemic sclerosis (SSc), spontaneous heart rate variability was investigated by means of time-domain and spectrum analysis of 24 h ECG ambulatory recordings in 30 SSc patients (four males, aged 45.2 +/- 9 yr, mean +/- S.D., range 27-60) and 30 age-matched healthy subjects. **A significantly higher heart rate (P < 0.01) and lower circadian and spectral indices of heart rate variability (P < 0.01) were observed in SSc patients, compared with controls. A predictive value of age (P = 0.002), tachycardia (P = 0.002), circadian heart rate variability (P = 0.0025) and spectral power values (P = 0.005) for patient mortality was found.** Moreover, the relative risk of death was higher (P = 0.05) in older subjects with circulating anti-Scl70. These abnormalities, detectable by a feasible, non-invasive diagnostic approach, indicate the presence of autonomic cardiac neuropathy in SSc patients.

Systemic Sclerosis

- **Prognosis**
- **Survival**
- Pathomorphosis

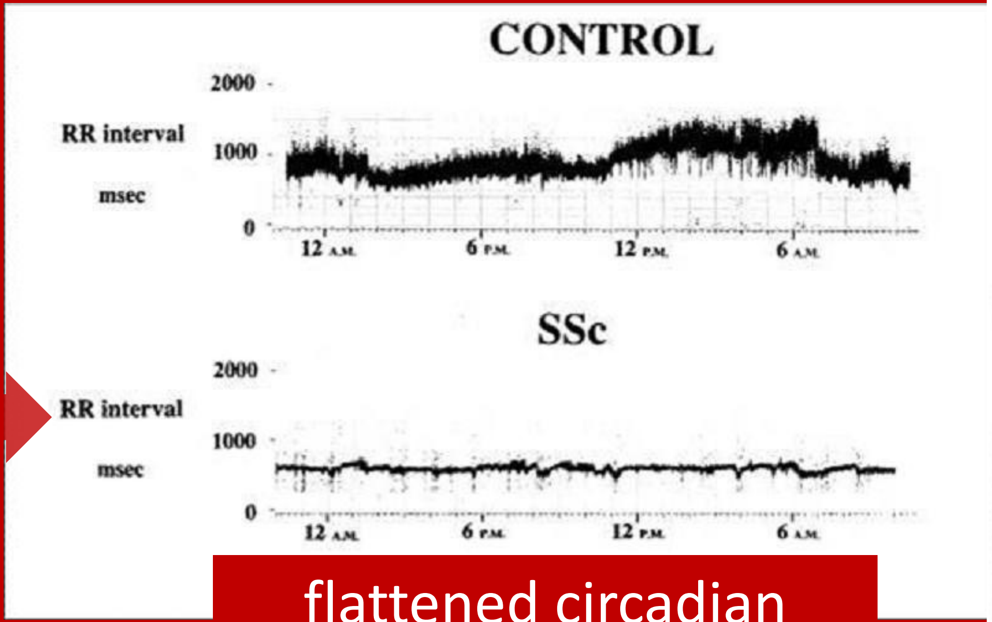
1997

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Autonomic dysfunction in systemic sclerosis: time and frequency domain 24 hour heart rate variability analysis

C Ferri[1], M Emdin, D Giuggioli, C Carpeggiani, M Maielli, A Varga, C Michelassi, G Pasero, A L'Abbate

Worst prognostic features:
- **tachycardia**
- **absence of nocturnal bradycardia**



flattened circadian heart rate variability

Controls SSc

Poor R-R spectrum

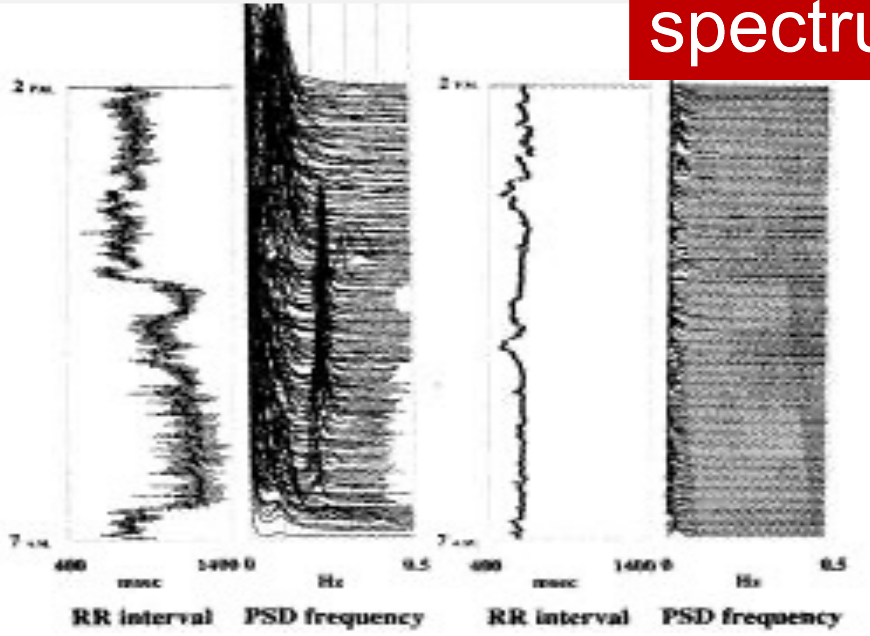


FIG. 1.—A normal spectral pattern (left) compared to a SSc patient one with particularly marked alterations (right). From left to right: RR interval mean ± S.D. computed over each spectrum (left columns) and respective power spectra (normalization = 50 000 ms²) are shown over a 17 h period, beginning at 2 p.m. and ending at 7 p.m., containing sleep time. As compared to the control, the SSc patient shows tachycardia, the disappearance of nocturnal bradycardia and an extremely 'poor' RR spectrum, with very small LF peaks, with the disappearance of the nocturnal increase in HF spectral component.

2002

Prognostic role of Heart involvement in SSc patients

Frequent cause of death

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Systemic Sclerosis

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TABLE 6. Causes of death

No. of patients deceased	279/915	(30.4%)
Females/males	5.3	(235/44)
Causes of Death	No.	(%)
Unknown	109	
Known	170	
Heart involvement	62	(36)
Lung involvement	40	(24)
Heart + lung involvement	15	(9)
Cancer	25	(15)
Kidney involvement	21	(12)
Miscellaneous	7	(4)
SSc-related	36%	
Possibly SSc-related	52%	
Not SSc-related	12%	

Systemic Sclerosis

- **Prognosis**
- **Survival**
- Pathomorphosis

Systemic sclerosis

- Paraneoplastic manifestation

- Pre-neoplastic condition

Cancer
may severely affect the natural history
and outcome of SSc patients

Malignancies

- breast cancer
- lung cancer
- thyroid cancer
- thymus neoplasms
- gynecological malignancies

SSc and Cancer

Thymus neoplasms

Rheumatology 2006;45:72–75
doi:10.1093/rheumatology/kei101
Advance Access publication 27 September 2005

Concise Report

Thymus alterations and systemic sclerosis

C. Ferri, M. Colaci, L. Battolla[1], D. Giuggioli and M. Sebastiani

Objectives. The pathogenesis of systemic sclerosis (SSc) includes complex alterations to the immune system, possibly responsible for diffuse microvasculature and fibroblast dysfunction. Previous anecdotal observations suggest a possible role for thymus alterations in some autoimmune rheumatic diseases, including SSc. This study aimed to investigate the prevalence of radiological thymus alterations in SSc patients.

Methods. Thirthy-four unselected patients [28 female and 6 male, mean age (±S.D.) 49.7 ± 9.5 yr, range 33–67 yr] and 34 age- and sex-matched controls were included in the study. The presence of major radiological thymus alterations, i.e. an abnormally enlarged or nodular thymus, were blindly investigated by means of unenhanced multidetector computed tomography.

Results. Abnormally enlarged or nodular thymuses were detected in a statistically significant percentage of SSc patients compared with controls (21 *vs* 0%, $P = 0.011$). More interestingly, radiological thymus alterations were invariably observed in patients with shorter disease duration (≤5 yr, 41% *vs* >5 yr, 0%; $P = 0.007$), frequently associated with serum anti-Scl70 antibodies ($P = 0.017$). Among patients with thymus alterations one developed myasthenia gravis while two others showed thymus hyperplasia at histopathological evaluation after thymectomy.

Conclusions. The present study suggests a possible role of thymic disorders, mainly thymus hyperplasia, in a significant number of SSc patients. Due to the limitations of radiological evaluation, the actual relevance of such an association might be underestimated. The relationship of thymus alterations with shorter disease duration, as well as with serum anti-Scl70, suggests that thymic dysfunction could play a pathogenetic role mostly in the early phases of the disease, and possibly in specific SSc patient subsets.



A Moldavian 36 years-old man with limited cutaneous SSc since 2008 was referred to our Rheumatology Unit in June 2009. Radiological chest evaluation revealed subpleural groundglass opacities of the inferior lung lobes, pericardial effusion, and bilobed soft-tissue mass in anterior mediastinum, suggesting a neoplastic mass. The patient underwent a thymectomy in July 2009; the histopathological evaluation revealed a thymic hyperplasia.

In September 2010, the patient showed a marked worsening of the disease with diffuse cutaneous involvement SSc, melanodermia, and severe interstitial lung fibrosis involving the entire inferior lobes, which were scarcely responsive to pharmacological treatments (steroids and micophenolate mofetil).

In June 2011, he developed a Hodgkin's lymphoma responsible for the patient's death few months later.

793x732mm (72 x 72 DPI)

SSc and Cancer

TABLE 6. Causes of death

No. of patients deceased	279/915	(30.4%)
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Cancer	25	(15)
Kidney involvement	21	(12)
Miscellaneous	7	(4)
SSc-related	36%	
Possibly SSc-related	52%	
Not SSc-related	12%	

Ferri et al. Medicine 2002

Cancer 26%

Ferri et al. Autoimmunity Reviews 2014

SSc and Cancer

Autoimmunity Reviews xxx (2013) xxx–xxx

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Review

Breast cancer in systemic sclerosis: Results of a cross-linkage of an Italian Rheumatologic Center and a population-based Cancer Registry and review of the literature

Michele Colaci [a,*], Dilia Giuggioli [a], Caterina Vacchi [a], Federica Lumetti [a], Francesco Iachetta [b], Luigi Marcheselli [b], Massimo Federico [b], Clodoveo Ferri [a]

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ABSTRACT

Objective: Increased frequency of few types of cancer in systemic sclerosis (SSc) has been reported in the literature; in particular, breast carcinoma has been proposed as one of the most frequent malignancy in SSc patients, even though data are not univocal. The aim of the present study was to retrospectively evaluate the prevalence of breast cancer in our SSc series, compared with sex-/age-matched general population of the same geographical area, and the possible correlations with SSc features, including X-ray exposure for clinical investigations. A review of the world literature about this topic was also done.
Methods: Clinical records of 318 consecutive SSc patients, 31 M and 287 F, age 51.5 ± 14.5 SD years, disease duration 10 ± 6.5 SD years, referred to our Rheumatology Unit between January 2002 and December 2012 were evaluated.
Results: Twelve (3.8%) cases of breast cancer were recorded, including 11/287 females (3.8%) and 1/31 (3.2%) male patients. Considering the subgroup of 202 SSc patients resident in the Province of Modena compared with data of the local Tumor Registry, the incidence of breast cancer observed in our SSc series is significantly higher than expected (SIR 2.1; 95% interval of confidence: 1.13–3.90; p < 0.01). On the whole, the comparison between SSc patients with cancer and those without did not show any significant differences with regard to SSc clinical features, including the X-ray exposure. Of note is the relatively shorter disease duration at the time of breast cancer detection (median 2.5 years, range 1–21; disease duration of mean 10 ± 6.5 SD years in the entire cohort).
The review of the literature revealed that the observed incidence of breast cancer in our case series is comparable to the few studies reporting the highest percentages of this malignancy.
Conclusions: A significant increase of breast cancer incidence compared to sex–age-matched general population from the same geographic area was observed. Moreover, a close temporal relationship between SSc and breast cancer onset was found, independently from clinical, serological, and instrumental features of SSc. The possible pathogenetic link between this systemic autoimmune disease and complicating breast cancer, as well as the results of previous studies, are discussed.

SSc pts with BC
13 (0.6%)
2 (2.1%)
5 (1.9%)
5 (2
10 (
0
8 (1.
8 (3.
9 (1.
11 (
18 (
8 (2
5 (7.
0
28 (
8 (2
1 (0.
4 (1%)
11 (0.5%)
12 (3.8%)

= standardized i

Breast Cancer Incidence
SSc 3.8%
vs 2.1% controls

SSc and Cancer

Lung cancer

Autoimmunity Reviews 12 (2013) 374–379

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Autoimmunity Reviews

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Review

Lung cancer in scleroderma: Results from an Italian rheumatologic center and review of the literature☆

Michele Colaci [a,c], Dilia Giuggioli [a,c], Marco Sebastiani [a,c], Andreina Manfredi [a,c], Caterina Vacchi [a,c], Paolo Spagnolo [b,c], Stefania Cerri [b,c], Fabrizio Luppi [b,c], Luca Richeldi [b,c], Clodoveo Ferri [a,c,*]

[a] Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy
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ABSTRACT

The association between systemic sclerosis (SSc) and cancer was widely described, particularly with breast and lung carcinoma; while, data regarding possible associations between cancer and SSc features are still scarce. We retrospectively evaluated the prevalence of lung cancer in our SSc patient cohort (318 SSc patients, 31 M and 287 F, age 51.5± 14.5SD years, disease duration 10.3±6.5SD years) and clinico-serological factors potentially associated to the development of this malignancy. A review of the world literature about this topic was also done. We found that lung cancer complicated 16/318 (5%) SSc patients; namely 11/287 females (4%) and 5/31 males (16.1%). Median age of SSc patients with lung cancer was 54 (range 38–72) years for female patients, and 63 (range 40–73) for males; 13/16 patients died because of the neoplasia. Considering the incidence of lung carcinoma in sex/age-matched general population of the same geographical area, the percentages of lung cancer in our SSc series are about 2.5 and >5 times higher for male and female patients, respectively. The presence of lung cancer significantly correlated with male sex (p=0.011), presence of anti-Scl70 antibodies (p=0.0007), cyclophosphamide therapy (p=0.0001), forced vital capacity (FVC) <75% (p=0.0001), and lung fibrosis (p=0.0127); moreover patients with cancer have a significantly lower age at the diagnosis of SSc (p=0.009) and longer disease duration (p=0.0175). The logistic regression analysis confirmed a significant association with the anti-Scl70 antibodies (OR 6.4, 95%IC 1.7–24.1; p=0.006) and the reduction of FVC (OR 6.7, 95%IC 2.2–20.7; p=0.001) only. Overall, the prevalence of lung cancer in the subset of SSc patients with anti-Scl70 antibodies was 12/105 (11.4%), 9/40 (22.5%) in patients with FVC% reduction, and 7/22 (31.8%) in patients with both. In literature, the median prevalence of lung cancer in SSc series was 2.4% (range 0–4.2%); even if sporadic, associations with lung involvement or antiScl70 autoantibodies were raised, according to our findings.
Our study confirmed the higher frequency of lung cancer among SSc patients compared to general population, particularly within patients' subset with serum anti-Scl70 antibodies and lung involvement.

No lung cancer	%	Follow-up (years)	Associations
3	4.2	Mean 5	All pts with ILD
8	3	1335 pt-years	ILD
4	2.7	Not indicated	Scl70
7	2.8	2001 pt-years	ILD, age
5	2.1	Average 5.1	No
15	1.6	7403 pt-years	No
13	2.6	5–20	No
3	2.4	Median 4	No
7	2.8	Mean 5.8±4.2	No
12	2.7	5.5±3.1 (M) 6.1±2.8 (F)	No
10	1.8	>2	No
4	3.5	Mean 8.9	All female pts
0	0	Not indicated	No
2	0.7	Not indicated	No
40 (31[b])	1.8	6.4 (2.2–11.5)	No
2	0.9	Not indicated	No
21	1	1996–2008	No
16	5	3270 pt-years	Scl70, FVC <75%

5% vs 2.5%

Scl70+

SSc and Cancer

Rheumatology (Oxford). 2015 Sep 30.

Increased risk of papillary thyroid cancer in systemic sclerosis associated with autoimmune thyroiditis.

Antonelli A, Ferri C, Ferrari SM, Di Domenicantonio A, Giuggioli D, Galleri D, Miccoli P, Fallahi P.

Abstract

OBJECTIVES:
Patients with SSc have an increased risk of malignancy compared with the general population. Before now, no study has evaluated the risk of thyroid cancer (TC) in SSc patients. The aim of the study was to evaluate the prevalence of TC in SSc patients.
METHODS:
We studied the prevalence of TC in 327 unselected SSc patients in comparison with two population-based, gender- and age-matched control groups (654 subjects from an iodine-deficient area and 654 subjects from an iodine-sufficient area). Thyroid status was assessed by measurement of circulating thyroid hormones and autoantibodies, thyroid ultrasonography and fine-needle aspiration cytology (when necessary).
RESULTS:
Circulating thyroid-stimulating hormone, anti-thyroglobulin and anti-thyroperoxidase antibody levels, and the prevalence of hypothyroidism were significantly higher in SSc patients ($P < 0.01$, for all). Six patients with papillary TC (PTC) were detected among SSc patients, whereas only one case was observed in each of controls 1 and 2 ($P = 0.007$, for both). In SSc all patients with TC had evidence of thyroid autoimmunity vs 40% of the other SSc patients ($P = 0.001$).
CONCLUSION:
These data suggest a high prevalence of papillary TC in SSc patients, in particular in the presence of thyroid autoimmunity; careful thyroid monitoring would be opportune during the follow-up of these patients.

International Journal of Rheumatology Volume 2015, Article ID 761867, 5 pages http://dx.doi.org/10.1155/2015/761867

Research Article

Gynaecological Screening for Cervical and Vulvar Malignancies in a Cohort of Systemic Sclerosis Patients: Our Experience and Review of the Literature

M. Colaci,[1] D. Giuggioli,[1] G. Cassone,[1] C. Vacchi,[1] F. Campomori,[1] F. Boselli,[2] M. Sebastiani,[1] A. Manfredi,[1] and C. Ferri[1]

[1] *Chair and Rheumatology Unit, Medical School, Azienda Ospedaliero-Universitaria, Policlinico di Modena, University of Modena and Reggio Emilia, Via del Pozzo 71, 41100 Modena, Italy*

[2] *Institute of Obstetrics and Gynecology, Oncology Prevention Unit, University of Modena and Reggio Emilia, Modena, Italy*

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Received 19 August 2015; Revised 24 September 2015; Accepted 30 September 2015

Academic Editor: James R. Seibold

Background. Increased incidence of cancer was frequently reported in scleroderma (SSc), but no association with gynaecological malignancies was described in literature. *Objectives*. To investigate gynaecological neoplasms in SSc patients. *Methods*. In this cross-sectional analysis, we evaluated 80 SSc patients, living in the same geographical area. We considered all patients undergoing gynaecological evaluation, including pap test as screening for cervical cancer, between January 2008 and December 2014. *Results*. 55 (68.7%) patients were negative and 20 (25%) presented inflammatory alterations, while cancer or precancerous lesions were found in 5 (6.2%) cases (2 showed cervical cancer (one of them in situ), 1 vulvar melanoma, 1 vulvar intraepithelial neoplasia, and 1 endocervical polyp with immature squamous metaplasia). The frequency of cervical cancer in our series seems higher in comparison to the incidence registered in the same geographical area. The presence of atypical cytological findings correlated with anti-Scl70 autoantibodies ($p = 0.022$); moreover, the patients with these alterations tended to be older (median 65, range 46–67), if compared to the whole series ($p = 0.052$). *Conclusions*. A relatively high frequency of gynaecological malignancies was found in our SSc series. In general, gynaecological evaluation for SSc women needs to be included in the routine patients' surveillance.

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Printed in U.S.A.

Systemic Sclerosis

Demographic, Clinical, and Serologic Features and Survival in 1,012 Italian Patients

CLODOVEO FERRI, GABRIELE VALENTINI, FRANCO COZZI, MARCO SEBASTIANI, CLAUDIO MICHELASSI, GIOVANNI LA MONTAGNA, ARIANNA BULLO, MASSIMILIANO CAZZATO, ENRICO TIRRI, FRANCA STORINO, DILIA GIUGGIOLI, GIOVANNA CUOMO, MARA ROSADA, STEFANO BOMBARDIERI, SILVANO TODESCO, AND GIUSEPPE TIRRI, FOR THE SYSTEMIC SCLEROSIS STUDY GROUP OF THE ITALIAN SOCIETY OF RHEUMATOLOGY (SIR-GSSSC)*

Survival studies

published
before/after 1985
show that the prognosis of SSc
tends to improve over time

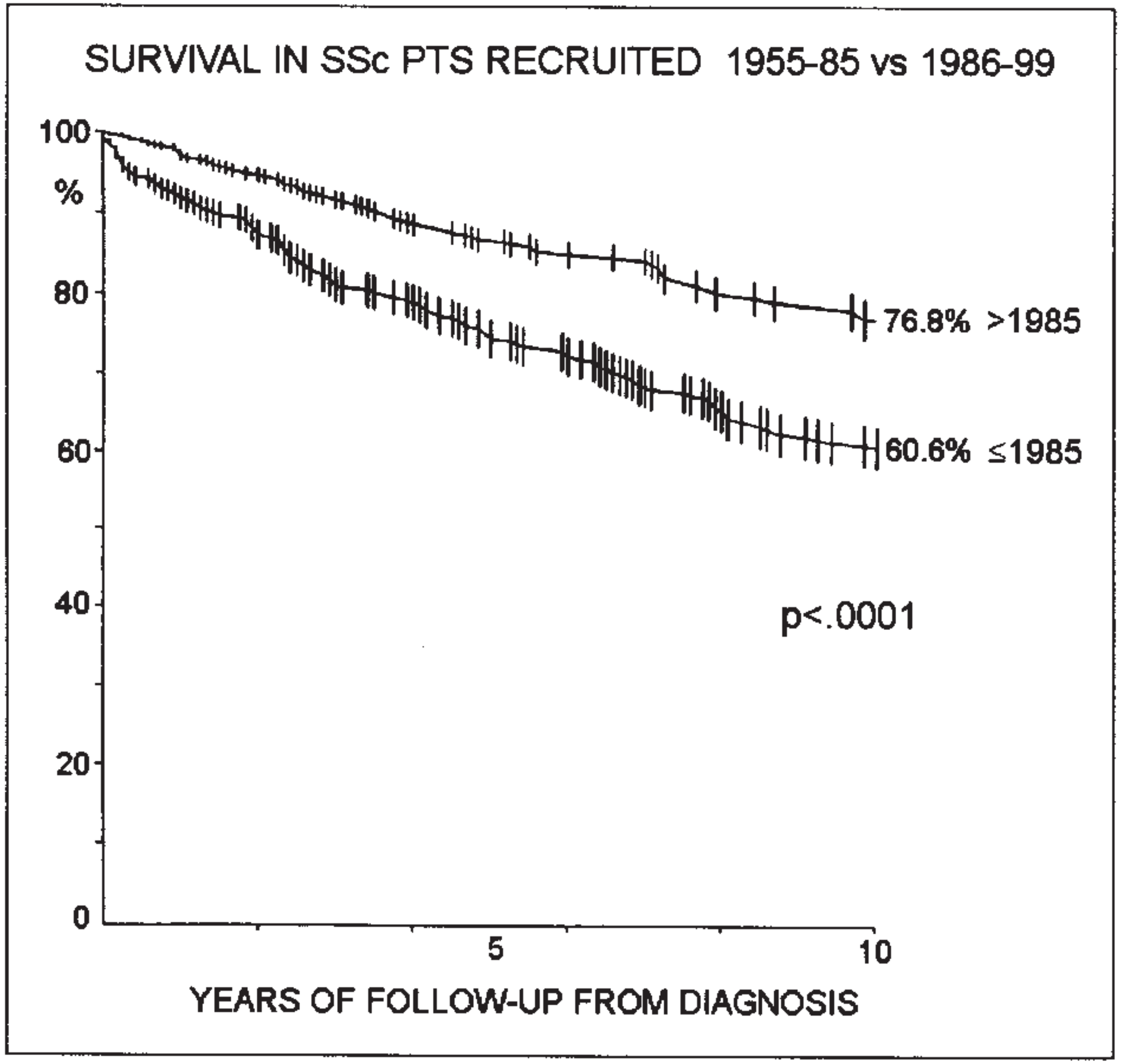


FIG. 9. Cumulative survival rates in patients recruited during 1955–1985 and 1986–1999, respectively.

Systemic Sclerosis

- Prognosis
- **Survival**
- Pathomorphosis



Ionian Sea



2014

Systemic Sclerosis

- Prognosis
- Survival
- **Pathomorphosis**

Autoimmunity Reviews xxx (2014) xxx–xxx

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journal homepage: www.elsevier.com/locate/autrev

ELSEVIER



Review

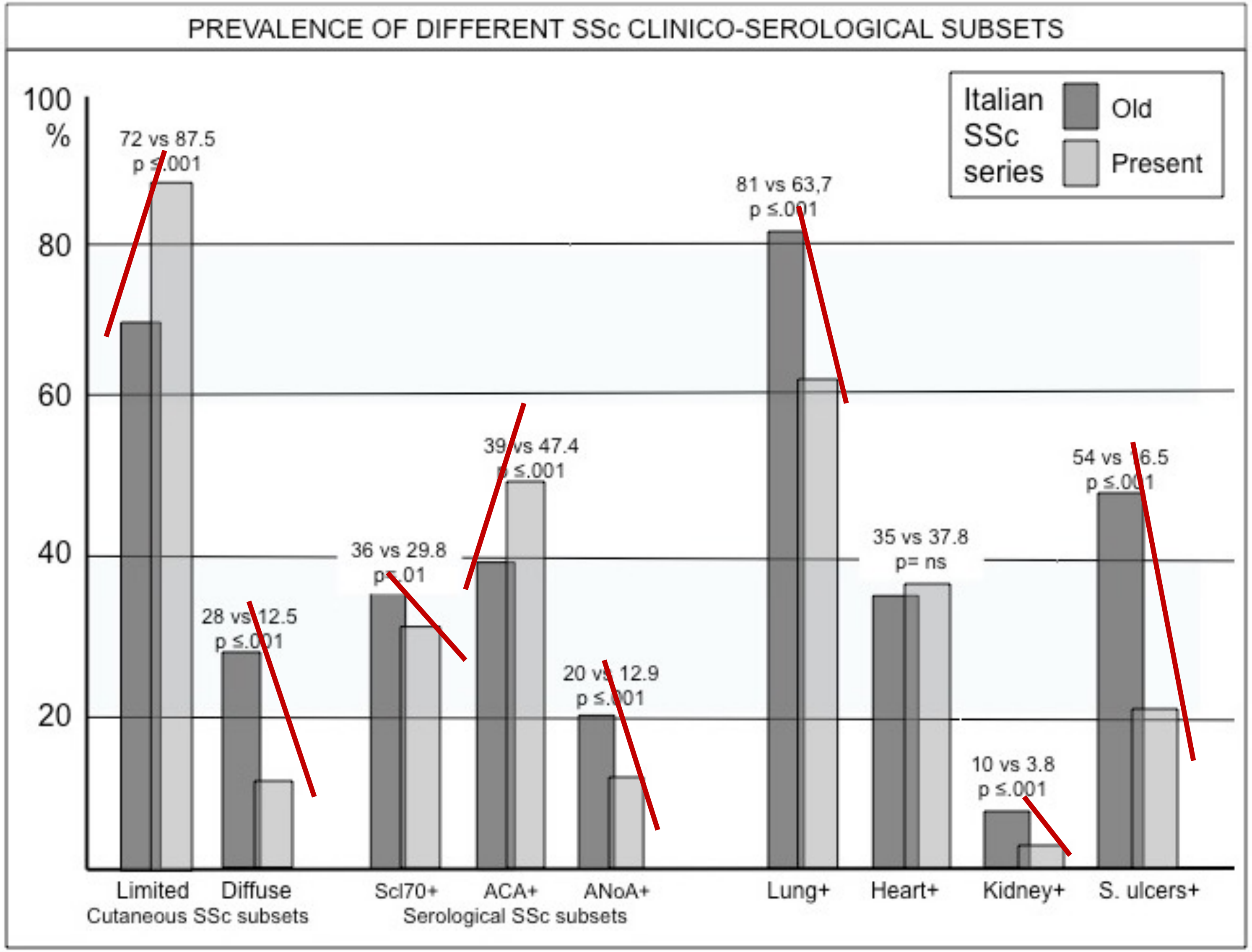
Systemic sclerosis evolution of disease pathomorphosis and survival. Our experience on Italian patients' population and review of the literature

Clodoveo Ferri [a,*], Marco Sebastiani [a], Andrea Lo Monaco [b], Michele Iudici [c], Dilia Giuggioli [a], Federica Furini [b], Andreina Manfredi [a], Giovanna Cuomo [c], Amelia Spinella [a], Michele Colaci [a], Marcello Govoni [b], Gabriele Valentini [c]

2014

Systemic Sclerosis

evolution of disease pathomorphosis and survival



Less severe clinico-serological composition of the disease in recent compared to old SSc series

Ferri C et al. Autoimmunity Rev 2014

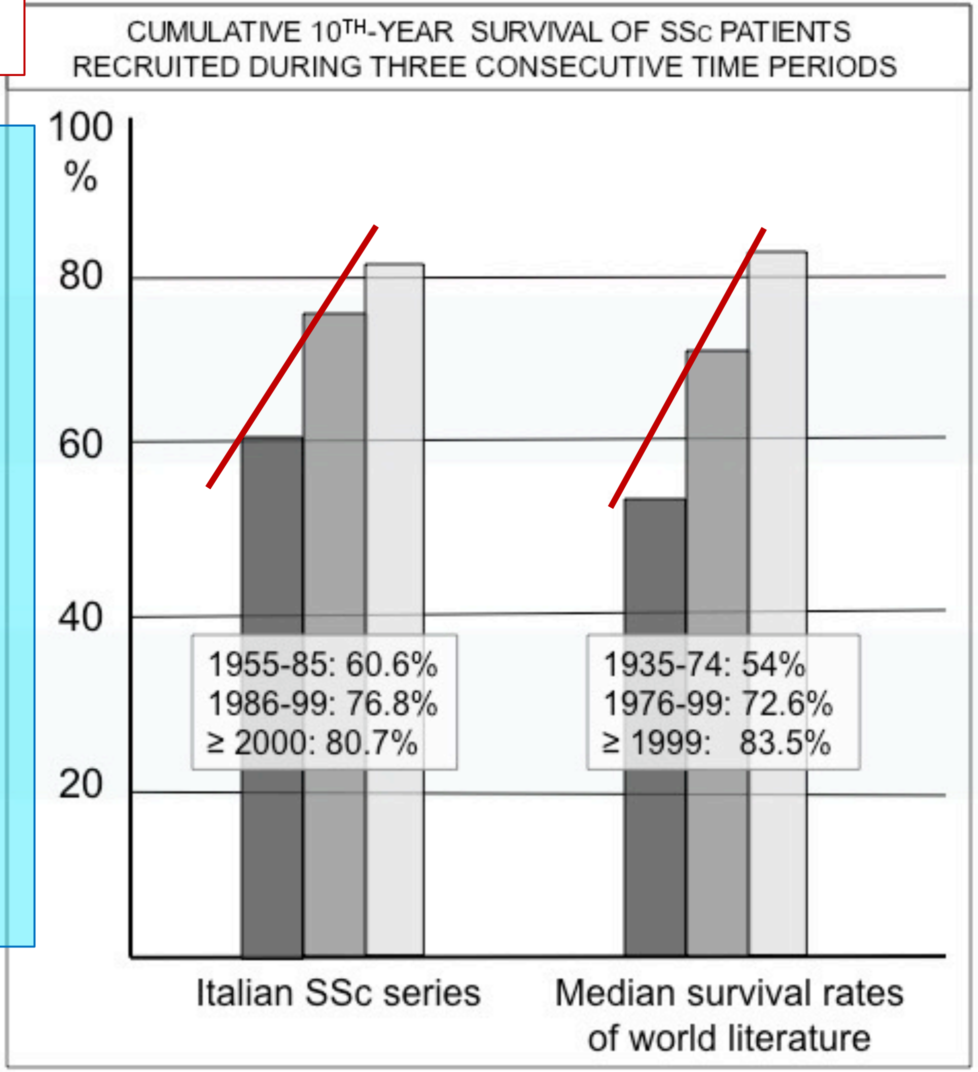
2014

Systemic Sclerosis
evolution of disease pathomorphosis and survival

Ferri et al. Autoimmmmunity Reviews 2014

10th -year Survival

Improved survival is possibly due to earlier referral/diagnosis, as well better treatments during the last years



Improved survival during the last 7 decades observed either in Italian and world literature SSc series

Systemic Sclerosis
evolution of disease pathomorphosis and survival

Ferri et al. Autoimmmmunity Rev 2014

- improved 10th year survival
- less frequent:
  - Diffuse cutaneous SSc
  - Lung inv.
  - heart inv.
  - Skin ulcers

Classification & treatment strategies of scleroderma skin ulcers

Autoimmunity Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

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Review

Scleroderma skin ulcers definition, classification and treatment strategies our experience and review of the literature

Dilia Giuggioli, Andreina Manfredi, Federica Lumetti, Michele Colaci, Clodoveo Ferri *

Autoimmunity Reviews xxx (2017) xxx–xxx

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Review

Scleroderma skin ulcers definition, classification and treatment strategies our experience and review of the literature

Dilia Giuggioli, Andreina Manfredi, Federica Lumetti, Michele Colaci, Clodoveo Ferri *

Fig. 2. Different subtypes of scleroderma skin ulcers (SSc-SU) according to proposed definition and classification criteria.
Digital ulcers (DU) of the hands or feet are the most frequent wound skin lesions of SSc; they may be complicated by gangrene.
DU with gangrene represent a very challenging condition that may be observed in a minority of patients with severe, non-healing DU of the hands or feet, or in some cases as presenting symptom at the patient's referral.
This latter occurrence needs a differential diagnosis with critical ischemia of the acral districts considering its relevant therapeutical implications (see text).
Some scleroderma skin lesions inconsistent with the diagnosis of SU/DU are shown in the bottom of the figure. SU: skin ulcer; DU: digital ulcer; SU on calcinosis: the arrows point small solid calcium lumps.





full moon

SPRING

Systemic sclerosis Progression INvestiGation

Coordinators:
Clodoveo Ferri - Marco Matucci Cerinic

SIR
Italian Society Rheumatology
Strategic Project

4 different cohorts:

1. Primary RP (pRP)
2. Suspected secondary RP
3. Very Early Diagnosis of SSc (VEDOSS)
4. Definite SSc

SPRING
Systemic sclerosis Progression INvestiGation

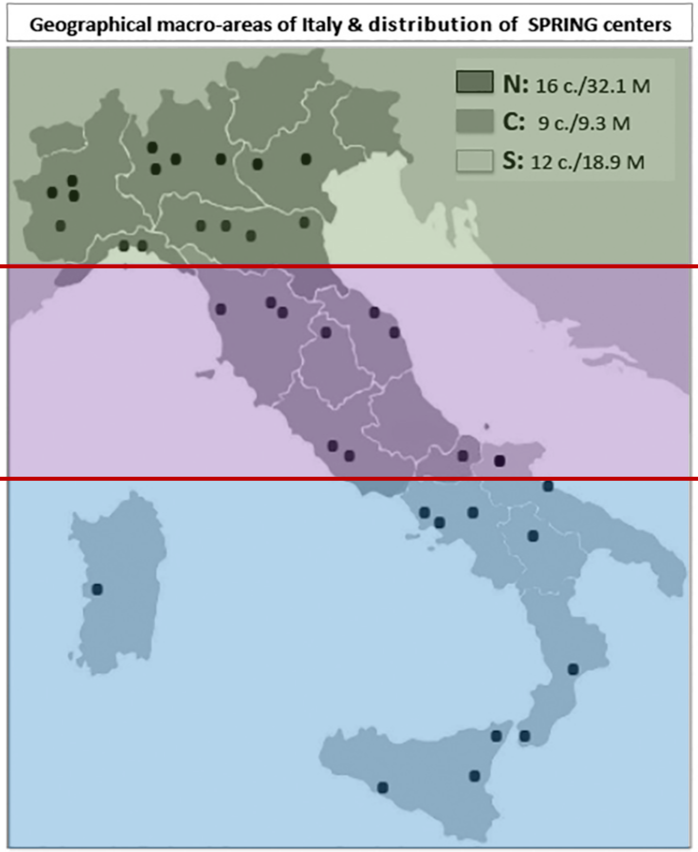


Fig. 1. Geographical macro-areas of Italy and distribution of centres participating to the SPRING registry. The three geographical macro-areas of Italy (N: Northern, C: Central, and S: Southern) showed a good relationship between the number of enrolled SSc patients (N: 814, C: 194, and S: 445), number/distribution of participating centres (N: 16 c., C: 9 c., and S: 12 c.) and resident general population (N: 32.1 Millions, C: 9.3 M, and S: 18.9 M).

Autoimmunity Reviews 21 (2022) 103159

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Geographical heterogeneity of clinical and serological phenotypes of systemic sclerosis observed at tertiary referral centres. The experience of the Italian SIR-SPRING registry and review of the world literature

Clodoveo Ferri [a,*], Rossella De Angelis [b], Dilia Giuggioli [a], Gianluigi Bajocchi [c], Lorenzo Dagna [d],

2022

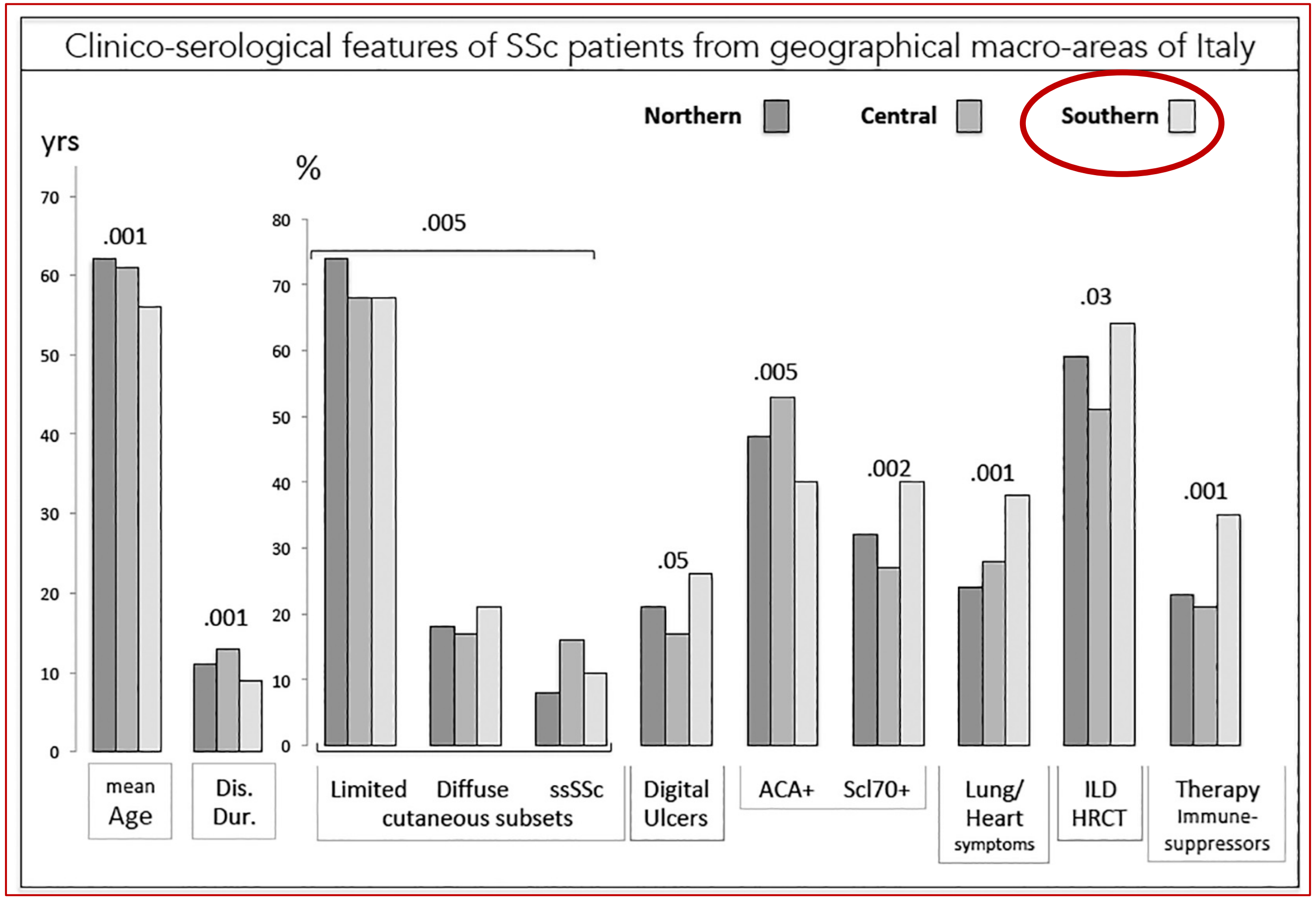
Conclusion:

The phenotypical differences among Italian macro-areas might be correlated to

- ➢ genetic/environmental co-factors, and/or
- ➢ **not equally distributed national network of information and healthcare facilities.**

2022 clinical and serological phenotypes of systemic sclerosis

Geographical heterogeneity



Patients living in Southern Italy were characterized by more severe clinical and/or serological SSc phenotypes compared to those living in Northern and Central Italy.

It is possibly due at least in part to a not equally distributed national network of information and healthcare facilities.

Ferri C et al. Autoimmunity Rev 2022



Camargue

Center for
Rare Lung Diseases

University of Modena & Reggio E.

Dir. C. Ferri
(2012-2017)

Studies on Interstitial Lung Disease (ILD) in Autoimmune Rheumatic Diseases

Relationship

- **Idiopathic ILD**
- **IPAF (interstitial pneumonia with autoimmune features)** → prevalent lung inv.
- **UCTD (unclassifiable connective tissue diseases)** → prevalent rheumatic autoimmune features
- **Systemic sclerosis & other ARDs (±ILD)**

multidisciplinary approach

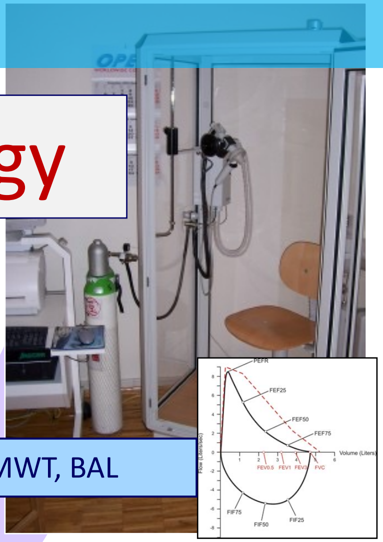
Others

- Internal Med.
- Immunology
- Infettivology
- Nutritional med.
- Grastroenterology
- Dermatology
- Occupational med.
- Physiatry
- Psychology

Lung & Heart



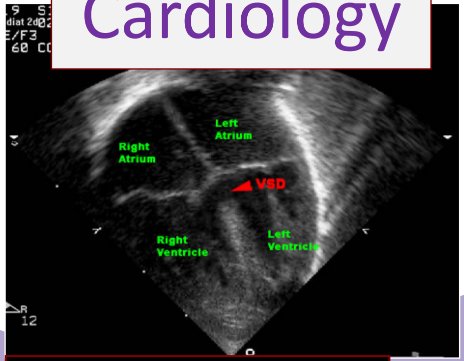
Pneumology



PFT, Dlco, 6-MWT, BAL

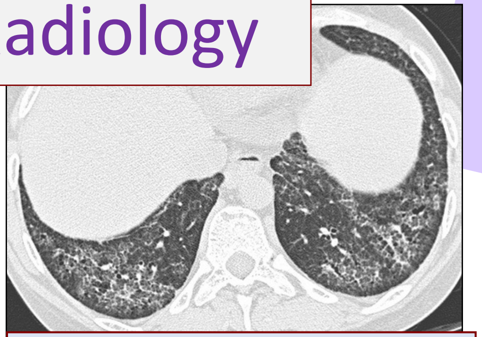
Rheumatology

Cardiology



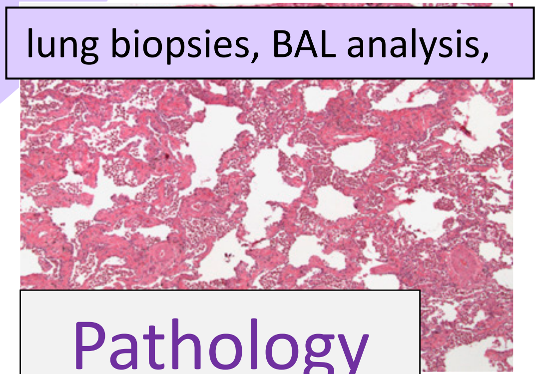
ECHO-Doppler, rigth heart catheter

Radiology



HRCT

lung biopsies, BAL analysis,



Pathology

2015 interstitial pneumonia with autoimmune features (IPAF)

Autoimmunity Reviews 15 (2016) 61–70

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Interstitial pneumonia with autoimmune features and undifferentiated connective tissue disease
Our interdisciplinary rheumatology–pneumology experience, and review of the literature

Clodoveo Ferri [a,*], Andreina Manfredi [a], Marco Sebastiani [a], Michele Colaci [a], Dilia Giuggioli [a], Caterina Vacchi [a], Giovanni Della Casa [c], Stefania Cerri [b], Pietro Torricelli [c], Fabrizio Luppi [b]

2015

IPAF vs UCTD

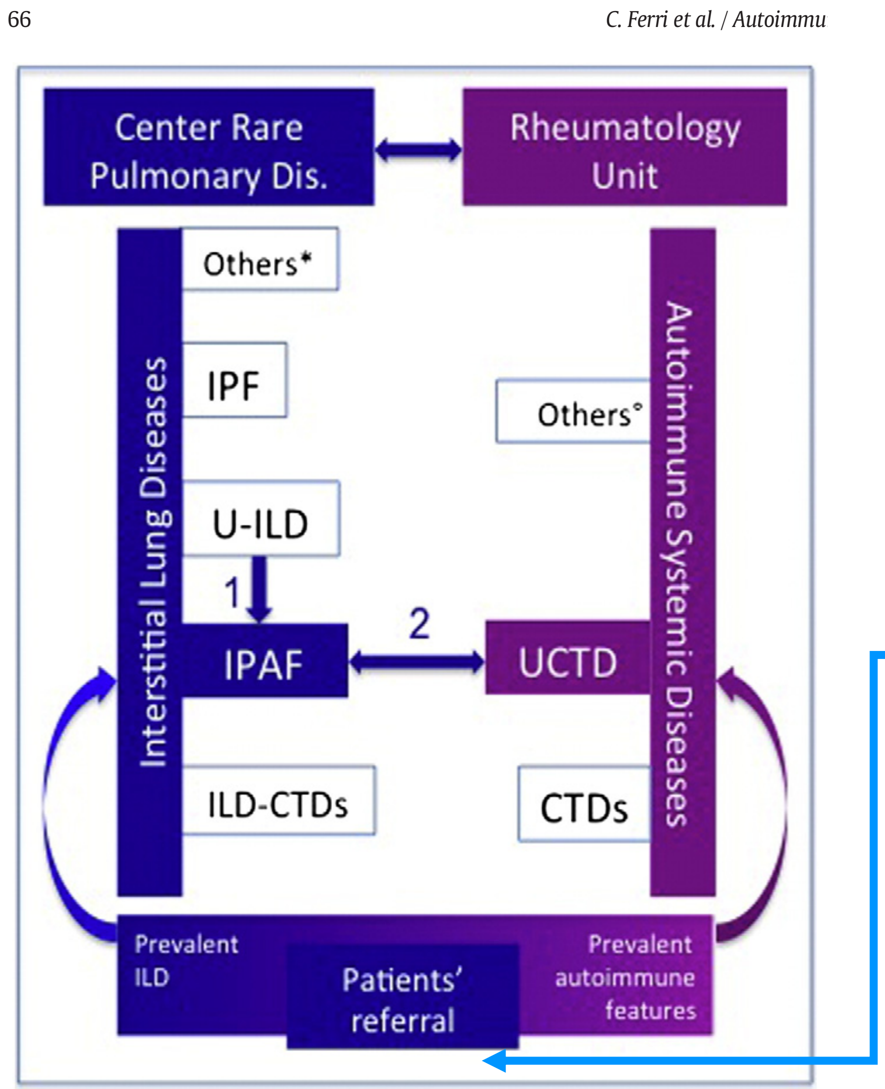


Fig. 1. At our center for the Rare Pulmonary Diseases there are referred patients with suspected interstitial lung diseases (ILDs) because of isolated/prevalent respiratory manifestations. They are evaluated by means of wide clinical work-up (Table 1) by trained pulmonologists and rheumatologists, with the contribution of other specialists, i.e. radiol- ogists, cardiologists, thoracic surgeon, and pathologists; the involved specialists have a long-term experience on the diagnosis and treatment of ILDs as well of CTDs and other au- toimmune diseases (AIDs) referred to our Rheumatology Unit. Patients were "nally classi- "ed according to guidelines and classi"cation criteria of international scienti"c societies (ref. 25–37). Besides established ILDs, CTDs, and AIDs, there are subjects with unclassifiable interstitial lung diseases (U-ILD).

These latter include a number of patients that fulfilled the recently proposed **'interstitial pneumonia with autoimmune features' (IPAF).** **The IPAF patients were compared with unclassifiable connective tissue diseases (UCTD) recruited among different CTDs and other AIDs referred to our Rheumatology Unit. There is a clear-cut clinic-serological overlapping between these two patients' series,** with the exception of ILD detectable in a very small percentage of UCTD patients (see Table 3).

This difference can be correlated to a

selection bias in the patients' referral:

subjects with clinically dominant respiratory symptoms are invariably referred to tertiary pulmonary care unit, while patients with prevalent autoimmune features, with/without respiratory symptoms, are commonly referred to rheumatologists (see also Fig. 2). *Exposure related ILD (occupational, environmental, avocational, medication, smoking), sarcoidosis, idio- pathic ILD [respiratory bronchiolitis-associated-ILD (RB-ILD), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), lymphocytic interstitial pneumonia (LIP)], others (Langherans cell histiocytosis, eo- sinophilic pneumonia, neuro"bromatosis, lymphangioleiomyomatosis); IPF: idiopathic pulmonary fibrosis; °other systemic autoimmune diseases (AIDs): see Table 5.

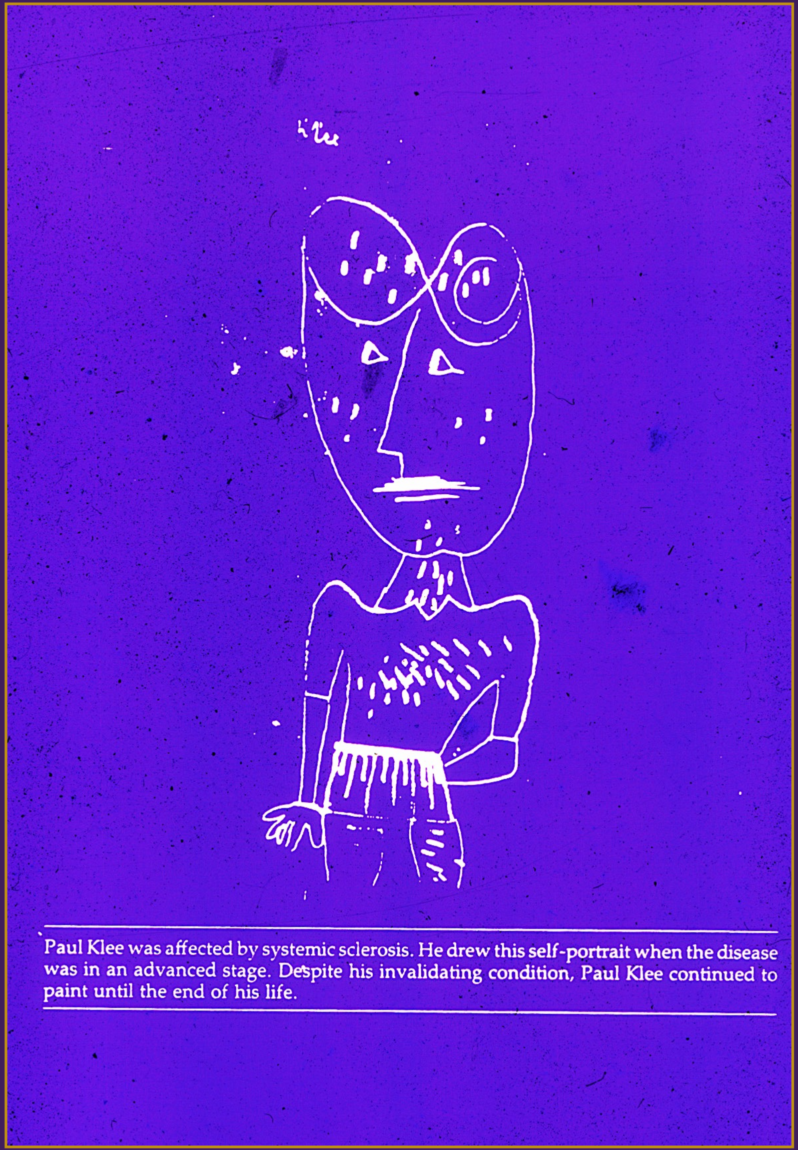
Ferri C et al Autoimmunity Rev 2015

Personae



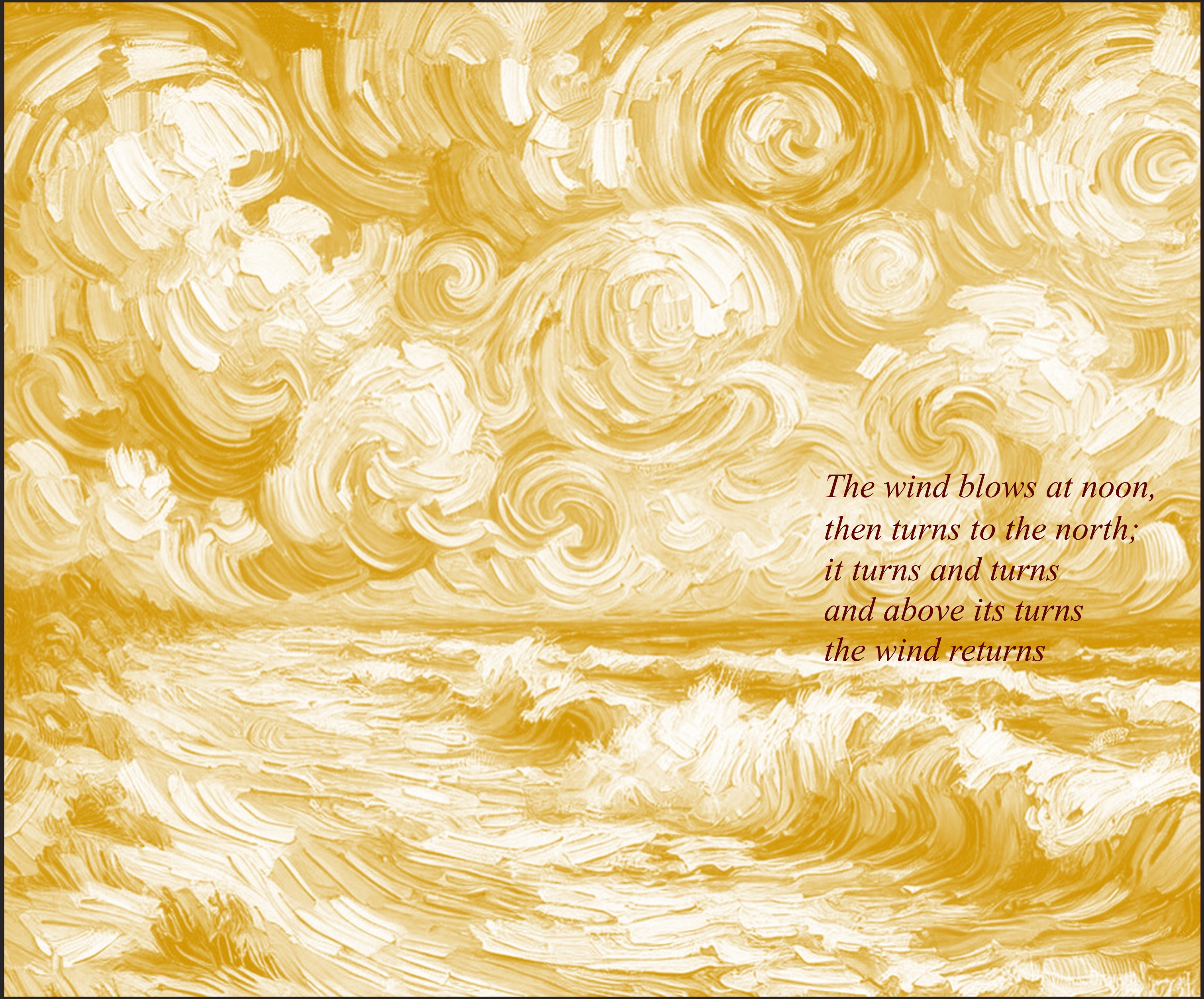
life is art





Paul Klee was affected by systemic sclerosis. He drew this self-portrait when the disease was in an advanced stage. Despite his invalidating condition, Paul Klee continued to paint until the end of his life.

art is life



Vanity of vanities,
says Qohelet.
Vanity of vanities,
all is vanity!